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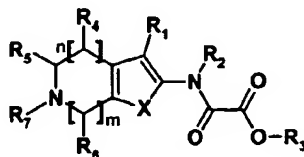
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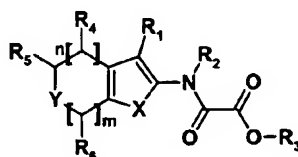(54) Title: MODULATORS OF PROTEIN TYROSINE PHOSPHATASES (PTPases)

(1)

(57) Abstract: The present invention provides novel compounds, novel compositions, methods of their use, and methods of their manufacture, where such compounds of Formula (1) are pharmacologically useful inhibitors of Protein Tyrosine Phosphatases (PTPase's) including PTP1B, T cell PTP, wherein n, m, X, R_1, R_2, R_3, R_4, R_5, R_6, and R_7 are defined more fully in the description. The compounds are useful in the treatment of type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance, obesity, and other diseases.

Modulators of Protein Tyrosine Phosphatases (PTPases)

5   **FIELD OF THE INVENTION**

The present invention relates to novel compounds, to methods for their preparation, to compositions comprising the compounds, to the use of these compounds as medicaments and their use in therapy, where such compounds of Formula 1 are pharmacologically useful inhi-

10 bitors of Protein Tyrosine Phosphatases (PTPases) such as PTP1B, CD45, SHP-1, SHP-2, PTPα, LAR and HePTP or the like,

Formula 1

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wherein n, m, X, Y, R_1, R_2, R_3, R_4, R_5 and R_6 are defined more fully below.

It has been found that PTPases plays a major role in the intracellular modulation and regulation of fundamental cellular signaling mechanisms involved in metabolism, growth, proliferation and differentiation (Hunter, Phil. *Trans. R. Soc. Lond.* B 353: 583-605 (1998); Chan *et*

20 *al., Annu. Rev. Immunol.* 12: 555-592 (1994); Zhang, *Curr. Top. Cell. Reg.* 35: 21-68 (1997); Matozaki and Kasuga, *Cell. Signal.* 8: 113-19 (1996); Flint *et al., The EMBO J.* 12:1937-46 (1993); Fischer *et al, Science* 253:401-6 (1991)). Overexpression or altered activity of tyrosine phosphatases can also contribute to the symptoms and progression of various diseases (Wiener, *et al., J. Natl. cancer Inst.* 86:372-8 (1994); Hunter and Cooper, *Ann. Rev. Biochem,*

25 54:897-930 (1985)). Furthermore, there is increasing evidence which suggests that inhibition of these PTPases may help treat certain types of diseases such as diabetes type I and II, autoimmune disease, acute and chronic inflammation, osteoporosis and various forms of cancer.

30 5252-263:1397-b-PTP-PTP-colony-*270*: 20824-16104 (1993), Brady-

Background of the Invention

Protein phosphorylation is now well recognized as an important mechanism utilized by cells to transduce and regulate signals during different stages of cellular function (Hunter, *Phil. Trans. R. Soc. Lond.* B *353*: 583-605 (1998); Chan *et al., Annu. Rev. Immunol. 12*: 555-592

5   (1994); Zhang, *Curr. Top. Cell. Reg. 35*: 21-68 (1997); Matozaki and Kasuga, *Cell. Signal. 8*: 113-19 (1996); Fischer *et al, Science 253*:401-6 (1991); Flint *et al., EMBO J. 12*:1937-46 (1993)). There are at least two major classes of phosphatases: (1) those that dephosphorylate proteins (or peptides) that contain a phosphate group(s) on a serine or threonine moiety (termed Ser/Thr phosphatases) and (2) those that remove a phosphate group(s) from the

10   amino acid tyrosine (termed protein tyrosine phosphatases or PTPases or PTPs).

The PTPases are a family of enzymes that can be classified into two groups: a) intracellular or nontransmembrane PTPases and b) receptor-type or transmembrane PTPases.

Intracellular PTPases: Most known intracellular type PTPases contain a single

15   conserved catalytic phosphatase domain consisting of 220-240 amino acid residues. The regions outside the PTPase domains are believed to play important roles in localizing the intracellular PTPases subcellularly (Mauro, L.J. and Dixon, J.E. *TIBS 19*: 151-155 (1994)). The first intracellular PTPase to be purified and characterized was **PTP1B**, which was isolated from human placenta (Tonks *et al., J. Biol. Chem. 263*: 6722-6730 (1988)). Shortly

20   after, PTP1B was cloned (Charbonneau *et al., Proc. Natl. Acad. Sci. USA 86*: 5252-5256 (1989); Chernoff *et al., Proc. Natl. Acad. Sci. USA 87*: 2735-2789 (1989)). Other examples of intracellular PTPases include (1) **T-cell PTPase/ TC-PTP** (Cool *et al. Proc. Natl. Acad. Sci. USA 86*: 5257-5261 (1989)), (2) **rat brain PTPase** (Guan *et al., Proc. Natl. Acad. Sci. USA 87*:1501-1502 (1990)), (3) neuronal phosphatase **STEP** (Lombroso *et al., Proc. Natl.*

25   *Acad. Sci. USA 88*: 7242-7246 (1991)), (4) ezrin-domain containing PTPases: **PTPMEG1** (Gu*et al., Proc. Natl. Acad. Sci. USA 88*: 5867-57871 (1991)), **PTPH1** (Yang and Tonks, *Proc. Natl. Acad. Sci. USA 88*: 5949-5953 (1991)), **PTPD1 and PTPD2** (Møller *et al., Proc. Natl. Acad. Sci. USA 91*: 7477-7481 (1994)), **FAP-1/BAS** (Sato *et al., Science 268*: 411-415 (1995); Banville *et al., J. Biol. Chem. 269*: 22320-22327 (1994); Maekawa *et al., FEBS*

30   *Letters 337*: 200-206 (1994)), and SH2 domain containing PTPases: **PTP1C/SH-PTP1/SHP-1** (Plutzky *et al., Proc. Natl. Acad. Sci. USA 89*: 1123-1127 (1992); Shen *et al., Nature Lond. 352*: 736-739 (1991)) and **PTP1D/Syp/SH-PTP2/SHP-2** (Vogel *et al., Science 259*: 1611-1614 (1993); Feng *et al., Science 259*: 1607-1611 (1993); Bastein *et al., Biochem. Biophys. Res. Comm. 196*: 124-133 (1993)).

35   *Receptor-type PTPases* consist of a) a putative ligand-binding extracellular domain, b) a transmembrane segment, and c) an intracellular catalytic region. The

structures and sizes of the putative ligand-binding extracellular domains of receptor-type PTPases are quite divergent. In contrast, the intracellular catalytic regions of receptor-type PTPases are very homologous to each other and to the intracellular PTPases. Most receptor-type PTPases have two tandemly duplicated catalytic PTPase domains.

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The first receptor-type PTPases to be identified were (1) **CD45/LCA** (Ralph, S.J., *EMBO J. 6*: 1251-1257 (1987)) and (2) **LAR** (Streuli *et al., J. Exp. Med. 168*: 1523-1530 (1988)) that were recognized to belong to this class of enzymes based on homology to PTP1B (Charbonneau *et al., Proc. Natl. Acad. Sci. USA 86*: 5252-5256 (1989)). CD45 is a family of

10   high molecular weight glycoproteins and is one of the most abundant leukocyte cell surface glycoproteins and appears to be exclusively expressed upon cells of the hematopoietic system (Trowbridge and Thomas, *Ann. Rev. Immunol. 12*: 85-116 (1994)).

The identification of CD45 and LAR as members of the PTPase family was quickly followed by identification and cloning of several different members of the receptor-type

15   PTPase group. Thus, 5 different PTPases, (3) **PTPα**, (4) **PTPβ**, (5) **PTPδ**, (6) **PTPε**, and (7) **PTPζ**, were identified in one early study (Krueger *et al., EMBO J. 9*: 3241-3252 (1990)). Other examples of receptor-type PTPases include (8) **PTPγ** (Barnea *et al., Mol. Cell. Biol. 13*: 1497-1506 (1995)) which, like **PTPζ** (Krueger and Saito, *Proc. Natl. Acad. Sci. USA 89*: 7417-7421 (1992)) contains a carbonic anhydrase-like domain in the extracellular region,

20   (9) **PTPμ** (Gebbink *et al., FEBS Letters 290*: 123-130 (1991)), (10) **PTPκ** (Jiang *et al., Mol. Cell. Biol. 13*: 2942-2951 (1993)). Based on structural differences the receptor-type PTPases may be classified into subtypes (Fischer *et al., Science 253*: 401-406 (1991)): (I) CD45; (II) LAR, PTPδ, (11) **PTPσ**; (III) **PTP** , (12) **SAP-1** (Matozaki *et al., J. Biol. Chem. 269*: 2075-2081 (1994)), (13) **PTP-U2/GLEPP1** (Seimiya *et al., Oncogene 10*: 1731-1738

25   (1995); Thomas *et al., J. Biol. Chem. 269*: 19953-19962 (1994)), and (14) **DEP-1**; (IV) **PTPα, PTPε**. All receptor-type PTPases except Type III contain two PTPase domains. Novel PTPases are continuously identified. In the early days of PTPase research, it was believed that the number of PTPs would match that of protein tyrosine kinases (PTKs) (Hanks and Hunter, *FASEB J. 9*: 576-596 (1995)). However, although about 90 open

30   reading frames in *C. elegans* contain the hallmark motif of PTPs, it now seems that the estimate of 'classical' PTPases must be downsized, perhaps to between 100 and 200 in humans. .

PTPases are the biological counterparts to protein tyrosine kinases Therefore, one important function of PTPases is to control, down-regulate, the activity of PTKs.

35   However, a more complex picture of the function of PTPases has emerged. Thus, several studies have shown that some PTPases may actually act as positive mediators of cellular

4

signaling. As an example, the SH2 domain-containing SHP-2 seems to act as a positive mediator in insulin-stimulated Ras activation (Noguchi *et al.*, *Mol. Cell. Biol. 14*: 6674-6682 (1994)) and of growth factor-induced mitogenic signal transduction (Xiao *et al.*, *J. Biol. Chem. 269*: 21244-21248 (1994)), whereas the homologous SHP-1 seems to act as a

5   negative regulator of growth factor-stimulated proliferation (Bignon and Siminovitch, *Clin.Immunol. Immunopathol. 73*: 168-179 (1994)). Another example of PTPases as positive regulators has been provided by studies designed to define the activation of the Src-family of tyrosine kinases. In particular, several lines of evidence indicate that CD45 is positively regulating the activation of hematopoietic cells, possibly through

10   dephosphorylation of the C-terminal tyrosine of Fyn and Lck (Chan *et al.*, *Annu. Rev. Immunol. 12*: 555-592 (1994)).

PTPases were originally identified and purified from cell and tissue lysates using a variety of artificial substrates and, therefore, their natural function of dephosphorylation was not well known. Since tyrosine phosphorylation by tyrosine kinases is usually associated with cell

15   proliferation, cell transformation and cell differentiation, it was assumed that PTPases were also associated with these events. This association has now been proven to be the case with many PTPases. PTP1B, a phosphatase whose structure was the first PTPase to be elucidated (Barford *et al.*, *Science* 263:1397-1404 (1994)) has been shown to be involved in insulin-induced oocyte maturation (Flint *et al.*, *The EMBO J.* 12:1937-46 (1993)) and it has been

20   suggested that the overexpression of this enzyme may be involved in p185$^{c\text{-}erb\,B2}$-associated breast and ovarian cancers (Wiener, *et al.*, *J. Natl. cancer Inst.* 86:372-8 (1994); Weiner *et al.*, *Am. J. Obstet. Gynecol.* 170:1177-883 (1994)). The association with cancer is recent evidence which suggests that overexpression of PTP1B is statistically correlated with increased levels of p185$^{c\text{-}erb\,B2}$ in ovarian and breast cancer. The role of PTP1B in the etiology and pro-

25   gression of the disease has not yet been elucidated. Inhibitors of PTP1B may therefore help clarify the role of PTP1B in cancer and in some cases provide therapeutic treatment for certain forms of cancer.

PTPases: the insulin receptor signaling pathway/diabetes

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Insulin is an important regulator of different metabolic processes and plays a key role in the control of blood glucose. Defects related to its synthesis or signaling lead to diabetes mellitus. Binding of insulin to the insulin receptor (IR) causes rapid (auto)phosphorylation of several tyrosine residues in the intracellular part of the β-subunit. Three closely positioned

35   tyrosine residues (the tyrosine-1150 domain) must all be phosphorylated to obtain full activity of the insulin receptor tyrosine kinase (IRTK) which transmits the signal further

downstream by tyrosine phosphorylation of other cellular substrates, including insulin receptor substrate-1 (IRS-1) (Wilden et al., J. Biol. Chem. 267: 16660-16668 (1992); Myers and White, Diabetes 42: 643-650 (1993); Lee and Pilch, Am. J. Physiol. 266: C319-C334 (1994); White et al., J. Biol. Chem. 263: 2969-2980 (1988)). The structural basis for the

5 function of the tyrosine-triplet has been provided by X-ray crystallographic studies of IRTK that showed tyrosine-1150 to be autoinhibitory in its unphosphorylated state (Hubbard et al., Nature 372: 746-754 (1994)) and of the activated IRTK (Hubbard, EMBO J. 16:5572-5581 (1997)).

Several studies clearly indicate that the activity of the auto-phosphorylated IRTK

10 can be reversed by dephosphorylation in vitro (reviewed in Goldstein, Receptor 3: 1-15 (1993); Mooney and Anderson, J. Biol. Chem. 264: 6850-6857 (1989)), with the tri-phosphorylated tyrosine-1150 domain being the most sensitive target for protein-tyrosine phosphatases (PTPases) as compared to the di- and mono- phosphorylated forms (King et al., Biochem. J. 275: 413-418 (1991)). This tyrosine-triplet functions as a control switch of

15 IRTK activity and the IRTK appears to be tightly regulated by PTP-mediated dephosphorylation in vivo (Khan et al., J. Biol. Chem. 264: 12931-12940 (1989); Faure et al., J. Biol. Chem. 267: 11215-11221 (1992); Rothenberg et al., J. Biol. Chem. 266: 8302-8311 (1991)). The intimate coupling of PTPases to the insulin signaling pathway is further evidenced by the finding that insulin differentially regulates PTPase activity in rat hepatoma

20 cells (Meyerovitch et al., Biochemistry 31: 10338-10344 (1992)) and in livers from alloxan diabetic rats (Boylan et al., J. Clin. Invest. 90: 174-179 (1992)).

Until recently, relatively little was known about the identity of the PTPases involved in IRTK regulation. However, the existence of PTPases with activity towards the insulin receptor can be demonstrated as indicated above. Further, when the strong

25 PTPase-inhibitor pervanadate is added to whole cells an almost full insulin response can be obtained in adipocytes (Fantus et al., Biochemistry 28: 8864-8871 (1989); Eriksson et al., Diabetologia 39: 235-242 (1995)) and skeletal muscle (Leighton et al., Biochem. J. 276: 289-292 (1991)). In addition, other studies show that a new class of peroxovanadium compounds act as potent hypoglycemic compounds in vivo (Posner et al.,supra). Two of

30 these compounds were demonstrated to be more potent inhibitors of dephosphorylation of the insulin receptor than of the EGF-receptor, thus indicating that even such relatively unselective inhibitors may convey some specificity in regulating different signal transduction pathways.

It was recently found by Montreal-based research groups that mice lacking the protein

35 tyrosine phosphatase-1B gene (PTP1B) (Elchebly et al., Science 283: 1544-1548 (1999)) yielded healthy mice that showed increased insulin sensitivity and resistance to diet-induced

6

obesity. Importantly, these results have been confirmed and extended independently by another research team from Boston (Klaman et al., Mol. Cell. Biol. 20: 5479-5489 (2000)). The enhanced insulin sensitivity of the PTP$^{-/-}$ mice was also evident in glucose and insulin tolerance tests. The PTP-1B knock-out mouse showed many characteristics which would be highly de-

5   sirable to have for an anti-diabetes treatment. Most importantly, the knock-out mice grew normally and were fertile and have exhibited no increased incidence of cancer, as obviously there could have been concerns when one considers the mitogenic properties of insulin. From the diabetes perspective, the first notable features of the knock-out animals were that blood glucose and insulin levels were lowered, and the consequent marked increase in insu-

10   lin sensitivity in the knock-out animals. Moreover, the insulin-stimulated tyrosine phosphorylation levels of IR and IRS-1 were found to be increased/prolonged in muscle and liver - but not in fat tissue. Thus, the main target tissues for this type of approach would appear to be insulin action in liver and muscle. This is in contrast to the main target tissue for the PPARγ agonist class of insulin sensitizers (the "-diones"), which is adipose tissue (Murphy & Nolan,

15   Exp. Opin. Invest. Drugs 9: 1347-1361 (2000)). Several other "diabetic" parameters were also improved, such as plasma triglycerides being decreased in the knock-out mice. However, perhaps even more remarkably and unexpectedly, the knock-out animals also exhibited a resistance to weight gain when placed on a high-fat diet. This is again in contrast to the action of the PPARγ agonist class of insulin sensitizers, which rather induce weight gain

20   (Murphy & Nolan, supra), and would suggest that inhibition of PTP-1B could be a particularly attractive option for treatment of obese Type II diabetics. This is also supported by the fact that the heterozygous mice from this study showed many of these desirable features. In the Montreal study, there appeared to be no gender differences, whereas in the Boston study in general the male animals had larger responses to PTP-1B being knocked out. In both studi-

25   es, the reduction in weight gain of the knock-out animals on the high fat diet was found to be due to a decreased fat cell mass, although differences were observed with respect to fat cell number. Leptin levels were also lower in the knock-out mice, presumably as a reflection of the decreased fat mass. Significantly, the Boston group also found that the knock-out animals had an increased energy expenditure of around 20% and an increased respiratory quo-

30   tient compared to the wild-type; again, heterozygote animals displayed an intermediate level of energy expenditure. Whether this increase in metabolic rate is a reflection of the effects of PTP-1B on insulin-signaling or on other cellular components remains to be established, but the bottom-line message that inhibition of this enzyme may be an effective anti-diabetic and perhaps also anti-obesity therapy is clear.

35   It should also be noted that in the PTP-1B knock-out mice the basal tyrosine phosphorylation level of the insulin receptor tyrosine kinase does not appear to be increased,

which is in contrast to the situation after insulin treatment where there is an increased or pro-longed phosphorylation. This might indicate that other PTPs are controlling the basic phosphorylation state of the insulin receptor in the knock-out mice – and perhaps in man.

Previous findings are in accordance with the results reported by Elchebly *et al.*
(supra) (recently reviewed in Kennedy, *Biomed. Pharmacother. 53*: 466-470 (1999)). Thus, it has been found that high glucose concentration induce insulin resistance and increase the expression of PTP1B in rat (fibroblasts expressing the human insulin receptor (Maegawa *et al., J. Biol. Chem. 270*: 7724-7730 (1995)). In rat L6 cells, insulin and insulin-like growth factor I (IGF-I) were found to induce increased PTPase activity, including increased PTP1B expression (Kenner *et al. J. Biol. Chem. 266*: 25455-25462 (1993)). In addition, the same group has shown that PTP1B may interact directly with the activated IR (Seely *et al. Diabetes 45*: 1379-1385 (1996)) and act directly as a negative regulator of insulin and IGF-I-stimulated signaling (Kenner *et al. J. Biol. Chem. 271*: 19810-19816 (1996)). Osmotic loading of rat KRC-7 hepatoma cells with neutralizing anti-PTP1B antibodies also indicated a role for PTP1B in negative regulating of the insulin signaling pathway (Akmad *et al. J. Biol. Chem. 270*: 20503-20508 (1995)).

Also other PTPases have been implicated as regulators of the insulin signaling pathway. Thus, it was found that the ubiquitously expressed SH2 domain containing PTPase, PTP1D/SHP-2 (Vogel *et al.*, 1993, *supra*), associates with and dephosphorylates IRS-1, but apparently not the IR itself (Kuhné *et al., J. Biol. Chem. 268*: 11479-11481 (1993); (Kuhné *et al., J. Biol. Chem. 269*: 15833-15837 (1994)).

Other studies suggest that receptor-type or membrane-associated PTPases are involved in IRTK regulation (Faure *et al., J. Biol. Chem. 267*: 11215-11221 (1992), (Häring *et al., Biochemistry 23*: 3298-3306 (1984); Sale, *Adv. Prot. Phosphatases 6*: 159-186 (1991)). Hashimoto *et al.* have proposed that LAR might play a role in the physiological regulation of insulin receptors in intact cells (Hashimoto *et al., J. Biol. Chem. 267*: 13811-13814 (1992)). Their conclusion was reached by comparing the rate of dephosphoryl-ation/inactivation of purified IR using recombinant PTP1B as well as the cytoplasmic domains of LAR and PTPα. Antisense inhibition was used to study the effect of LAR on insulin signaling in a rat hepatoma cell line (Kulas *et al., J. Biol. Chem. 270*: 2435-2438 (1995)). A suppression of LAR protein levels by about 60 percent was paralleled by an approximately 150 percent increase in insulin-induced auto-phosphorylation. However, only a modest 35 percent increase in IRTK activity was observed, whereas the insulin-dependent phosphatidylinositol 3-kinase (PI 3-kinase) activity was significantly increased by 350 percent. Reduced LAR levels did not alter the basal level of IRTK tyrosine phosphorylation or activity. The authors speculate that LAR could specifically

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dephosphorylate tyrosine residues that are critical for PI 3-kinase activation either on the insulin receptor itself or on a downstream substrate. Conflicting results have been reported for PTP-LAR knock-out mice. Thus, Goldstein and coworkers reported that transgenic mice deficient in PTP-LAR exhibit profound defects in glucose-homeostasis

5   (Ren et al., Diabetes 47: 493-497 (1998)). However, it is difficult to fully assess the contribution of LAR deficiency to the glucose homeostasis in these mice due to the fact that the control mice were of a different genetic background than the knock-out mice. Moreover, normal glucose homeostasis was reported in a different strain of PTP-LAR knock-out mice (Sorensen et al., Diabetologia 40: A143 (1997)).

10   While previous reports indicate a role of PTPα in signal transduction through src activation (Zheng et al., Nature 359: 336-339 (1992); den Hertog et al., EMBO J. 12: 3789-3798 (1993)) and interaction with GRB-2 (den Hertog et al., EMBO J. 13: 3020-3032 (1994); Su et al., J. Biol. Chem. 269: 18731-18734 (1994)), Møller, Lammers and coworkers provided results that suggest a function for this phosphatase and its close

15   relative PTP as negative regulators of the insulin receptor signal (Møller et al., 1995 supra;

Lammers, et al. , FEBS Lett. 404:37-40 (1997). These studies also indicated that receptor-like PTPases might play a significant role in regulating the IRTK.

Other studies have shown that PTP1B and TC-PTP are likely to be involved in the

20   regulation of several other cellular processes in addition to the described regulatory roles in insulin signaling. Therefore, PTP1B and/or TC-PTP as well as other PTPases showing key structural features with PTP1B and TC-PTP are likely to be important therapeutic targets in a variety of human and animal diseases. The compounds of the present invention are useful for modulating or inhibiting PTP1B and/or TC-PTP and/or other PTPases showing

25   key structural features with said PTPases and for treating diseases in which said modulation or inhibition is indicated. A few examples that are not intended in any way to limit the scope of the invention of substrates that may be regulated by PTP1B will be given below.

Tonks and coworkers have developed an elegant 'substrate trapping' technique

30   that has allowed identification of the epidermal growth factor receptor (EGF-R) as a major substrate of PTP1B in COS cells (Flint et al. Proc. Natl. Acad. Sci. USA 94: 1680-1685 (1997)). In addition, three other as yet unidentified substrates of PTP1B were isolated. As an example of these studies, it has been found - using the above substrate-trapping technique - that PTP1B in addition to the EGF-R associates with activated platelet-derived

35   growth factor receptor (PDGF-R), but not with colony-stimulating factor 1 receptor (CSF-1R) (Liu & Chernoff, Biochem. J. 327: 139-145 (1997)).

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Early studies have shown that the subcellular localization as well as the enzyme activity of PTP1B may be regulated by agonist-induced calpain-catalyzed cleavage in human platelets (Frangioni *et al. EMBO J. 12:* 4843-4856 (1993)). Moreover, PTP1B cleavage correlated with the transaction from reversible to irreversible platelet aggregation.

5   Thus, as a non-limiting example compounds of the present invention might be used to prevent or induce irreversible platelet aggregation in individuals in need thereof. It was proposed that the cleavage-induced change in the subcellular localization of PTP1B (from membrane to cytosol) results in different substrate specificity not only in platelet but also in other cell types (Frangioni *et al.*, supra).

10   The above substrate trapping method has further been used to identify the protein tyrosine kinase p210$^{bcr-abl}$ as a substrate for PTP1B (LaMontagne, Jr. *et al. Mol. Cell. Biol. 18:* 2965-2975 (1998)). These studies suggest that PTP1B might function as a negative regulator of p210$^{bcr-abl}$ signaling *in vivo*. In addition, PTP1B was recently found to bind to and dephosphorylate the docking protein p130^{Cas} in rat fibroblasts and thereby suppress

15   transformation by v-crk, v-src, and v-ras, but not by v-raf (Liu *et al. Mol. Cell. Biol. 18:* 250-259 (1998)).

The transmembrane PTPase CD45, which is believed to be hematopoietic cell-specific, was found to negatively regulate the insulin receptor tyrosine kinase in the human multiple myeloma cell line U266 (Kulas *et al., J. Biol. Chem. 271:* 755-760 (1996)).

20   Further, PTPases influences the following hormones or diseases or disease states: somatostatin, the immune system/autoimmunity, cell-cell interactions/cancer, platelet aggregation, osteoporosis, and microorganisms, as disclosed in PCT Publication WO 99/15529 .

Somatostatin inhibits several biological functions including cellular proliferation

25   (Lamberts *et al., Molec. Endocrinol. 8:* 1289-1297 (1994)). While part of the antiproliferative activities of somatostatin are secondary to its inhibition of hormone and growth factor secretion (e.g. growth hormone and epidermal growth factor), other antiproliferative effects of somatostatin are due to a direct effect on the target cells. As an example, somatostatin analogs inhibit the growth of pancreatic cancer presumably via stimulation of a single

30   PTPase, or a subset of PTPases, rather than a general activation of PTPase levels in the cells (Liebow *et al., Proc. Natl. Acad. Sci. USA 86:* 2003-2007 (1989); Colas *et al., Eur. J. Biochem. 207:* 1017-1024 (1992)).

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PTPases: the immune system/autoimmunity

Several studies suggest that the receptor-type PTPase CD45 plays a critical role not only for initiation of T cell activation, but also for maintaining the T cell receptor-mediated

5   signaling cascade. These studies are reviewed in: (Weiss A., *Ann. Rev. Genet. 25*: 487-510 (1991); Chan *et al., Annu. Rev. Immunol. 12*: 555-592 (1994); Trowbridge and Thomas, *Annu. Rev. Immunol. 12*: 85-116 (1994)).

CD45 is one of the most abundant of the cell surface glycoproteins and is expressed exclusively on hemopoetic cells. In T cells, it has been shown that CD45 is one of the critical

10   components of the signal transduction machinery of lymphocytes. In particular, evidence has suggested that CD45 phosphatase plays a pivotal role in antigen-stimulated proliferation of T lymphocytes after an antigen has bound to the T cell receptor (Trowbridge, *Ann. Rev. Immunol*, 12: 85-116 (1994)). Several studies suggest that the PTPase activity of CD45 plays a role in the activation of Lck, a lymphocyte-specific member of the Src family protein-tyrosine

15   kinase (Mustelin etal., *Proc. Natl. Acad. Sci. USA 86*: 6302-6306 (1989); Ostergaard *et al., Proc. Natl. Acad. Sci. USA 86*: 8959-8963 (1989)). These authors hypothesized that the phosphatase activity of CD45 activates Lck by dephosphorylation of a C-terminal tyrosine residue, which may, in turn, be related to T-cell activation. Thus, it was found that recombinant p56lck specifically associates with recombinant CD45 cytoplasmic domain protein, but

20   not to the cytoplasmic domain of the related PTPα (Ng et al., *J. Biol. Chem. 271*: 1295-1300 (1996)). The p56lck-CD45 interaction seems to be mediated via a nonconventional SH2 domain interaction not requiring phosphotyrosine. In immature B cells, another member of the Src family protein-tyrosine kinases, Fyn, seems to be a selective substrate for CD45 compared to Lck and Syk (Katagiri et al., *J. Biol. Chem. 270*: 27987-27990 (1995)).

25   Studies using transgenic mice with a mutation for the CD45-exon6 exhibited lacked mature T cells. These mice did not respond to an antigenic challenge with the typical T cell mediated response (Kishihara *et al., Cell 74*:143-56 (1993)). Inhibitors of CD45 phosphatase would therefore be very effective therapeutic agents in conditions that are associated with autoimmune diseases with rheumatoid arthritis, systemic lupus erythematosus, type I diabe-

30   tes, and inflammatory bowel disease as non-limiting examples. Another important use of CD45 inhibitors is for immunosuppression in connection with tissue or cell transplantation and other condtions with need for immunosuppressive treatment.

CD45 has also been shown to be essential for the antibody mediated degranulation of mast cells (Berger *et al., J. Exp. Med. 180*:471-6 (1994)). These studies were also done

35   with mice that were CD45-deficient. In this case, an IgE-mediated degranulation was demonstrated in wild type but not CD45-deficient T cells from mice. These data suggest that CD45

11

inhibitors could also play a role in the symptomatic or therapeutic treatment of allergic disorders with asthma, allergic rhinitis, food allergy, eczema, urticaria and anaphylaxis as non-limiting examples.

Another PTPase, an inducible lymphoid-specific protein tyrosine phosphatase
5   (HePTP) has also been implicated in the immune response. This phosphatase is expressed in both resting T and B lymphocytes, but not non-hemopoetic cells. Upon stimulation of these cells, mRNA levels from the HePTP gene increase 10-15 fold (Zanke *et al.*, *Eur. J. Immunol.* *22*: 235-239 (1992)). In both T and B cells HePTP may function during sustained stimulation to modulate the immune response through dephosphorylation of specific residues. Its exact
10   role, however remains to be defined.

Likewise, the hematopoietic cell specific SHP-1 seems to act as a negative regulator and play an essential role in immune cell development.In accordance with the above-mentioned important function of CD45, HePTP and SHP-1, selective PTPase inhibitors may be attractive drug candidates both as immunosuppressors and as immunostimulants. Recent
15   studies illustrate the potential of PTPase inhibitors as immunmodulators by demonstrating the capacity of the non-selective vanadium-based PTPase inhibitor, BMLOV, to induce apparent B cell selective apoptosis compared to T cells (Dawson *et al.*, *FEBS Lett.* 478: 233-236; Schieven *et al.*, *J. Biol. Chem. 270*: 20824-20831 (1995)).

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PTPases: cell-cell interactions/cancer

Focal adhesion plaques, an *in vitro* phenomenon in which specific contact points are formed when fibroblasts grow on appropriate substrates, seem to mimic, at least in part, cells and their
25   natural surroundings. Several focal adhesion proteins are phosphorylated on tyrosine residues when fibroblasts adhere to and spread on extracellular matrix (Gumbiner, *Neuron 11:* 551-564 (1993)). However, aberrant tyrosine phosphorylation of these proteins can lead to cellular transformation. The intimate association between PTPases and focal adhesions is supported by the finding of several intracellular PTPases with ezrin-like N-terminal domains, e.g. PTPMEG1
30   (Gu *et al., Proc. Natl. Acad. Sci. USA 88*: 5867-5871 (1991), PTPH1 (Yang and Tonks, *Proc. Natl. Acad. Sci. USA 88*: 5949-5953 (1991)) and PTPD1 (Møller *et al., Proc. Natl. Acad. Sci. USA 91*: 7477-7481 (1994)). The ezrin-like domain shows similarity to several proteins that are believed to act as links between the cell membrane and the cytoskeleton. PTPD1 was found to be phosphorylated by and associated with c-src *in vitro* and is hypothesized to be involved in
35   the regulation of phosphorylation of focal adhesions (Møller *et al., supra*).

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PTPases may oppose the action of tyrosine kinases, including those responsible for phosphorylation of focal adhesion proteins, and may therefore function as natural inhibitors of transformation. TC-PTP, and especially the truncated form of this enzyme (Cool *et al., Proc. Natl. Acad. Sci. USA 87:* 7280-7284 (1990)), can inhibit the transforming

5   activity of v-*erb* and v-*fms* (Lammers *et al., J. Biol. Chem. 268:* 22456-22462 (1993), Zander *et al., Oncogene 8:* 1175-1182 (1993)). Moreover, it was found that transformation by the oncogenic form of the *HER2/neu* gene was suppressed in NIH 3T3 fribroblasts overexpressing PTP1B (Brown-Shimer *et al., Cancer Res. 52:* 478-482 (1992)).

The expression level of PTP1B was found to be increased in a mammary cell line

10   transformed with *neu* (Zhay *et al., Cancer Res. 53:* 2272-2278 (1993)). The intimate relationship between tyrosine kinases and PTPases in the development of cancer is further evidenced by the finding that PTPε is highly expressed in murine mammary tumors in transgenic mice over-expressing c-*neu* and v-Ha-*ras*, but not c-*myc* or *int-2* (Elson and Leder, *J. Biol. Chem. 270:* 26116-26122 (1995)). Further, the human gene encoding PTPγ

15   was mapped to 3p21, a chromosomal region, which is frequently deleted in renal and lung carcinomas (LaForgia *et al., Proc. Natl. Acad. Sci. USA 88:* 5036-5040 (1991)).

In this context, it seems significant that PTPases appear to be involved in controlling the growth of fibroblasts. Thus, it was found that Swiss 3T3 cells harvested at high density contain a membrane-associated PTPase whose activity on an average is 8-

20   fold higher than that of cells harvested at low or medium density (Pallen and Tong, *Proc. Natl. Acad. Sci. USA 88:* 6996-7000 (1991)). It was hypothesized by the authors that density-dependent inhibition of cell growth involves the regulated elevation of the activity of the PTPase(s) in question. In accordance with this view, a membrane-bound, receptor-type PTPase, DEP-1, showed enhanced (>=10-fold) expression levels with increasing cell

25   density of WI-38 human embryonic lung fibroblasts and in the AG1518 fibroblast cell line (Östman *et al., Proc. Natl. Acad. Sci. USA 91:* 9680-9684 (1994)).

Two closely related receptor-type PTPases, PTPκ and PTPμ, can mediate homophilic cell-cell interaction when expressed in non-adherent insect cells, suggesting that these PTPases might have a normal physiological function in cell-to-cell signalling

30   (Gebbink *et al., J. Biol. Chem. 268:* 16101-16104 (1993), Brady-Kalnay *et al., J. Cell Biol. 122:* 961-972 (1993); Sap *et al., Mol. Cell. Biol. 14:* 1-9 (1994)). Interestingly, PTPκ and PTPμ do not interact with each other, despite their structural similarity (Zondag *et al., J. Biol. Chem. 270:* 14247-14250 (1995)). From the studies described above it is apparent that PTPases may play an important role in regulating normal cell growth. However, as

35   pointed out above, other studies indicate that PTPases may also function as positive mediators of intracellular signaling and thereby induce or enhance mitogenic responses.

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Increased activity of certain PTPases might therefore result in cellular transformation and tumor formation. Indeed, in one study over-expression of PTPα was found to lead to transformation of rat embryo fibroblasts (Zheng, *supra*). In addition, SAP-1 was found to be highly expressed in pancreatic and colorectal cancer cells. SAP-1 is mapped to

5   chromosome 19 region q13.4 and might be related to carcinoembryonic antigen mapped to 19q13.2 (Uchida *et al., J. Biol. Chem. 269*: 12220-12228 (1994)). Further, the dsPTPase, cdc25, dephosphorylates cdc2 at Thr14/Tyr-15 and thereby functions as positive regulator of mitosis (reviewed by Hunter, *Cell 80*: 225-236 (1995)). Inhibitors of specific PTPases are therefore likely to be of significant therapeutic value in the treatment of certain forms of

10   cancer.

PTPases: platelet aggregation

PTPases seem to be centrally involved in platelet aggregation. Thus, agonist-induced

15   platelet activation results in calpain-catalyzed cleavage of PTP1B with a concomitant 2-fold stimulation of PTPase activity (Frangioni *et al., EMBO J. 12*: 4843-4856 (1993)). The cleavage of PTP1B leads to subcellular relocation of the enzyme and correlates with the transition from reversible to irreversible platelet aggregation in platelet-rich plasma. In addition, the SH2 domain containing PTPase, SHP-1, was found to translocate to the

20   cytoskeleton in platelets after thrombin stimulation in an aggregation-dependent manner (Li *et al., FEBS Lett. 343*: 89-93 (1994)).

     Although some details in the above two studies have been questioned, there is over-all agreement that PTP1B and SHP-1 play significant functional roles in platelet aggregation (Ezumi *et al., J. Biol. Chem. 270*: 11927-11934 (1995)). In accordance with

25   these observations, treatment of platelets with the PTPase inhibitor pervanadate leads to significant increase in tyrosine phosphorylation, secretion and aggregation (Pumiglia *et al., Biochem. J. 286*: 441-449 (1992)).

PTPases: osteoporosis

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The rate of bone formation is determined by the number and the activity of osteoblasts, which in term are determined by the rate of proliferation and differentiation of osteoblast progenitor cells, respectively. Histomorphometric studies indicate that the osteoblast number is the primary determinant of the rate of bone formation in humans (Gruber *et al.,*

35   *Mineral Electrolyte Metab. 12*: 246-254 (1987), reviewed in Lau *et al., Biochem. J. 257*: 23-36 (1989)). Acid phosphatases/PTPases may be involved in negative regulation of

14

osteoblast proliferation. Thus, fluoride, which has phosphatase inhibitory activity, has been found to increase spinal bone density in osteoporotics by increasing osteoblast proliferation (Lau et al., supra). Consistent with this observation, an osteoblastic acid phosphatase with PTPase activity was found to be highly sensitive to mitogenic concentrations of fluoride

5   (Lau et al., J. Biol. Chem. 260: 4653-4660 (1985), Lau et al., J. Biol. Chem. 262: 1389-1397 (1987), Lau et al., Adv. Protein Phosphatases 4: 165-198 (1987)). Interestingly, the level of membrane-bound PTPase activity was increased dramatically when the osteoblast-like cell line UMR 106.06 was grown on collagen type-I matrix compared to uncoated tissue culture plates. Since a significant increase in PTPase activity was observed in density-dependent

10   growth arrested fibroblasts (Pallen and Tong, Proc. Natl. Acad. Sci. 88: 6996-7000 (1991)), it might be speculated that the increased PTPase activity directly inhibits cell growth. The mitogenic action of fluoride and other phosphatase inhibitors (molybdate and vanadate) may thus be explained by their inhibition of acid phosphatases/PTPases that negatively regulate the cell proliferation of osteoblasts. The complex nature of the involvement of

15   PTPases in bone formation is further suggested by the identification of a novel parathyroid regulated, receptor-like PTPase, OST-PTP, expressed in bone and testis (Mauro et al., J. Biol. Chem. 269: 30659-30667 (1994)). OST-PTP is up-regulated following differentiation and matrix formation of primary osteoblasts and subsequently down-regulated in the osteoblasts which are actively mineralizing bone in culture. It may be hypothesized that

20   PTPase inhibitors may prevent differentiation via inhibition of OST-PTP or other PTPases thereby leading to continued proliferation. This would be in agreement with the above-mentioned effects of fluoride and the observation that the tyrosine phosphatase inhibitor orthovanadate appears to enhance osteoblast proliferation and matrix formation (Lau et al., Endocrinology 116: 2463-2468 (1988)). In addition, it was observed that vanadate, vanadyl

25   and pervanadate all increased the growth of the osteoblast-like cell line UMR106. Vanadyl and pervanadate were stronger stimulators of cell growth than vanadate. Only vanadate was able to regulate the cell differentiation as measured by cell alkaline phosphatase activity (Cortizo et al., Mol. Cell. Biochem. 145: 97-102 (1995)). It is of particular interest to the current invention that several studies have shown that bisphosphonates, such as

30   alendronate and tiludronate, inhibit the PTPase activity in osteoclasts, and that the inhibition of PTPase activity correlated with the inhibition of in vitro osteoclast formation and boneresorption (Schmidt et al., Proc. Natl. Acad. Sci. U.S.A. 93: 3068-3073 (1996); Murakami et al., Bone 20: 399-404 (1997); Opas et al., Biochem. Pharmacol. 54: 721-727 (1997); Skorey et al., J. Biol. Chem. 272: 22472-22480 (1997)). Thus, PTPase inhibitors –

35   other than bisphophonates – can potentially be effective for prevention and/or treatment of osteoporosis.
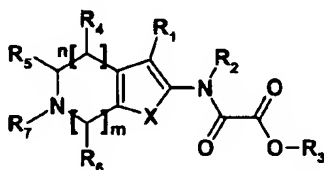
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PTPases: microorganisms

Dixon and coworkers have called attention to the fact that PTPases may be a key element

5   in the pathogenic properties of *Yersinia* (reviewed in Clemens *et al. Molecular Microbiology*
5: 2617-2620 (1991)). This finding was rather surprising since tyrosine phosphate is
thought to be absent in bacteria. The genus *Yersinia* comprises 3 species: *Y. pestis*
(responsible for the bubonic plague), *Y. pseudoturberculosis* and *Y. enterocolitica* (causing
enteritis and mesenteric lymphadenitis). Interestingly, a dual-specificity phosphatase, VH1,

10   has been identified in Vaccinia virus (Guan *et al., Nature 350*: 359-263 (1991)). These
observations indicate that PTPases may play critical roles in microbial and parasitic
infections, and they further point to PTPase inhibitors as a novel, putative treatment
principle of infectious diseases.

     WO 99/46267 discloses compounds which are pharmacologically useful inhibitors of

15   PTPases. However, the present invention which represents a novel selection under WO
99/46267, discloses a class of compounds which surprisingly are more potent against protein
tyrosine phosphatases (e.g. PTP1B) than those disclosed in WO 99/46267.

DESCRIPTION OF THE INVENTION

20   The present invention relates to Compounds of the Formula 1 wherein n, m, X, R_1, R_2, R_3,
R_4, R_5 and R_8 are defined below;

Formula 1

25   In the above Formula 1
n is 0, 1 or 2;
m is 1 or 2;
X is S or O ;

30   R_1 is hydrogen, $COOR_3$, or R_1 is selected from the group consisting of the following 5-
membered heterocycles:

16

R_2 is hydrogen, C_1-C_6alkyl, hydroxy or NR_8R_9;

R_3 is hydrogen, C_1-C_6alkyl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyloxyC_1-C_6alkyl or C_1-C_6alkylcarbonyloxyarylC_1-C_6alkyl;

R_4, R_5 and R_6 are independently hydrogen, trihalomethyl, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, oxo, carboxy, carboxyC_1-C_6alkyl, C_1-C_6alkyloxy-carbonyl, aryloxycarbonyl, arylC_1-C_6alkyloxycarbonyl, C_1-C_6alkyloxy, C_1-C_6alkyloxyC_1-C_6alkyl, aryloxy, arylC_1-C_6alkyloxy, arylC_1-C_6alkyloxyC_1-C_6alkyl, thio, C_1-C_6alkylthio, C_1-C_6alkylthioC_1-C_6alkyl, arylthio, arylC_1-C_6alkylthio, arylC_1-C_6alkylthioC_1-C_6alkyl, NR_8R_9, $R_8R_9NC_1$-C_6alkyl, C_1-C_6alkylaminoC_1-C_6alkyl, arylaminoC_1-C_6alkyl, arylC_1-C_6alkylaminoC_1-C_6alkyl, di(arylC_1-C_6alkyl)aminoC_1-C_6alkyl, C_1-C_6alkylcarbonyl, C_1-C_6alkyl-carbonylC_1-C_6alkyl, arylC_1-C_6alkylcarbonyl, arylC_1-C_6alkylcarbonylC_1-C_6alkyl, C_1-C_6alkylcarboxy, C_1-C_6alkylcarboxyC_1-C_6-alkyl, arylcarboxy, arylcarboxyC_1-C_6alkyl, arylC_1-C_6alkylcarboxy, arylC_1-C_6alkylcarboxyC_1-C_6alkyl, C_1-C_6alkylcarbonylamino, C_1-C_6alkylcarbonylaminoC_1-C_6alkyl, arylcarbonylaminoC_1-C_6alkyl, -carbonylNR_8C_1-C_6alkylCOR_{12}, arylC_1-C_6alkylcarbonylamino, arylC_1-C_6alkylcarbonylaminoC_1-C_6alkyl, $CONR_8R_9$, or C_1-C_6alkyl$CONR_8R_9$ wherein the alkyl and aryl groups are optionally substituted and R_{12} is NR_8R_9, or C_1-C_6alkylNR_8R_9;

R_7 is hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, C_1-C_6alkyloxocarbonyl, arylcarbonyl, aryloxocarbonyl, arylC_1-C_6alkylcarbonyl, arylC_1-C_6alkyloxocarbonyl, C_1-C_6alkylcarboxy, arylC_1-C_6alkylcarboxy, $R_{10}R_{11}$NcarbonylC_1-C_6alkyl wherein R_{10} and R_{11} are independently selected from hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, arylcarbonyl, arylC_1-C_6alkylcarbonyl, C_1-C_6alkylcarboxy or arylC_1-C_6alkyl-carboxy; wherein the alkyl and aryl groups are optionally substituted;

17

R_8 and R_9 are independently selected from hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, C_1-C_6alkyloxocarbonyl, arylcarbonyl, aryloxocarbonyl, arylC_1-C_6alkylcarbonyl, arylC_1-C_6alkyloxocarbonyl, C_1-C_6alkylcarboxy, arylC_1-C_6alkylcarboxy, $R_{10}R_{11}$NcarbonylC_1-C_6alkyl wherein the alkyl and aryl groups are optionally substituted; or

5   R_8 and R_9 are together with the nitrogen to which they are attached forming a saturated, partially saturated or aromatic cyclic, bicyclic or tricyclic ring system containing from 3 to 14 carbon atoms and from 0 to 3 additional heteroatoms selected from nitrogen, oxygen or sulphur, the ring system can optionally be substituted with at least one C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, oxo, C_1-C_6alkyloxy, arylC_1-C_6alkyloxy, C_1-C_6alkyloxyC_1-C_6alkyl, $NR_{10}R_{11}$ or C_1-

10   C_6alkylaminoC_1-C_6alkyl, wherein R_{10} and R_{11} are independently selected from hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, arylcarbonyl, arylC_1-C_6alkylcarbonyl, C_1-C_6alkylcarboxy or arylC_1-C_6alkylcarboxy; wherein the alkyl and aryl groups are optionally substituted; or

R_8 and R_9 are independently a saturated or partial saturated cyclic 5, 6 or 7 membered ami-

15   ne, imide or lactam;

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form,.or prodrug thereof.

20   The compounds of the invention can be further modified to act as prodrugs.

It is a well known problem in drug discovery that compounds, such as enzyme inhibitors, may be very potent and selective in biochemical assays, yet be inactive in vivo. This lack of so-called bioavailability may be ascribed to a number of different factors such as lack of or poor absorption in the gut, first pass metabolism in the liver, poor uptake in cells. Al-

25   though the factors determining bioavailability are not completely understood, there are many examples in the scientific literature - well known to those skilled in the art - of how to modify compounds, which are potent and selective in biochemical assays but show low or no activity in vivo, into drugs that are biologically active. It is within the scope of the invention to modify the compounds of the invention, termed the 'original compound', by attaching chemical

30   groups that will improve the bioavailability of said compounds in such a way that the uptake in cells or mammals is facilitated. Examples of said modifications, which are not intended in any way to limit the scope of the invention, include changing of one or more carboxy groups to esters (for instance methyl esters, ethyl esters, acetoxymethyl esters or other acyloxymethyl esters). Compounds of the invention, original compounds, such modified by attaching

35   chemical groups are termed 'modified compounds'. Said chemical groups may or may not be apparent in the claims of this invention. Other examples of modified compounds, which are

18

not intended in any way to limit the scope of the invention, are compounds that have been cyclized at specific positions - socalled 'cyclic compounds' - which upon uptake in cells or mammals become hydrolyzed at the same specific position(s) in the molecule to yield the compounds of the invention, the original compounds, which are then said to be 'non-cyclic'.

5   For the avoidance of doubt, it is understood that the latter original compounds in most cases will contain other cyclic or heterocyclic structures that will not be hydrolyzed after uptake in cells or mammals. Generally, said modified compounds will not show a behaviour in biochemical assays similar to that of the original compound, i.e. the corresponding compounds of the invention without the attached chemical groups or said modifications. Said modified

10   compounds may even be inactive in biochemical assays. However, after uptake in cells or mammals these attached chemical groups of the modified compounds may in turn be removed spontaneously or by endogenous enzymes or enzyme systems to yield compounds of the invention, original compounds. 'Uptake' is defined as any process that will lead to a substantial concentration of the compound inside cells or in mammals. After uptake in cells or

15   mammals and after removal of said attached chemical group or hydrolysis of said cyclic compound, the compounds may have the same structure as the original compounds and thereby regain their activity and hence become active in cells and/or in vivo after uptake. A . number of procedures, well known to those skilled in the art, may be used to verify that the attached chemical groups have been removed or that the cyclic compound has been hydro-

20   lyzed after uptake in cells or mammals. An example, which is not intended in any way to limit the scope of the invention, is given in the following. A mammalian cell line, which can be obtained from the American Tissue Type Collection or other similar governmental or commercial sources, is incubated with said modified compound. After incubation at conditions well known to those skilled in the art, the cells are washed appropriately, lysed and the lysate is

25   isolated. Appropriate controls, well known to those skilled in the art, must be included. A number of different procedures, well known to those skilled in the art, may in turn be used to extract and purify said compound from said lysate. Said compound may or may not retain the attached chemical group or said cyclic compound may or may not have been hydrolyzed. Similarly, a number of different procedures - well known to those skilled in the art - may be

30   used to structurally and chemically characterize said purified compound. Since said purified compound has been isolated from said cell lysate and hence has been taken up by said cell line, a comparison of said structurally and chemically characterized compound with that of the original unmodified compound (i.e. without said attached chemical group or said non-cyclic compound) will immediately provide those skilled in the art information on whether the

35   attached chemical group as been removed in the cell or if the cyclic compound has been hydrolyzed. As a further analysis, said purified compound may be subjected to enzyme kinetic

analysis as described in detail in the present invention. If the kinetic profile is similar to that of the original compound without said attached chemical group, but different from said modified compound, this confirms that said chemical group has been removed or said cyclic compounds has been hydrolyzed.Similar techniques may be used to analyze compounds of the invention in whole animals and mammals.

A preferred prodrug is acetoxymethyl esters of the compounds of the present invention which may be prepared by the following general procedure *(C.Schultz et al, The Journal of Biological Chemistry, 1993, 268, 6316-6322.)*:

A carboxylic acid (1 equivalent) is suspended in dry acetonitrile (2 ml per 0.1 mmol). Diisopropyl amine (3.0 equivalents) is added followed by bromomethyl acetate (1.5 equivalents). The mixture is stirred under nitrogen overnight at room temperature. Acetonitrile is removed under reduced pressure to yield an oil which is diluted in ethylacetate and washed with water (3 x). The organic layer is dried over anhydrous magnesium sulfate. Filtration followed by solvent removal under reduced pressure afford a crude oil. The product is purified by column chromatography on silica gel, using an appropriate solvent system.

DEFINITIONS

As used herein, the term "attached" or "-" (e.g. -COR_{11} which indicates the carbonyl attachment point to the scaffold) signifies a stable covalent bond, certain preferred points of attachment points being apparent to those skilled in the art.

The terms "halogen" or "halo" include fluorine, chlorine, bromine, and iodine.

The term "alkyl" includes C_1-C_6 straight chain saturated, methylene and C_2-C_6 unsaturated aliphatic hydrocarbon groups, C_1-C_6 branched saturated and C_2-C_6 unsaturated aliphatic hydrocarbon groups, C_3-C_6 cyclic saturated and C_5-C_6 unsaturated aliphatic hydrocarbon groups, and C_1-C_6 straight chain or branched saturated and C_2-C_6 straight chain or branched unsaturated aliphatic hydrocarbon groups substituted with C_3-C_6 cyclic saturated and unsaturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, this definition shall include but is not limited to methyl (Me), ethyl (Et), propyl (Pr), butyl (Bu), pentyl, hexyl, heptyl, ethenyl, propenyl, butenyl, penentyl, hexenyl, isopropyl (i-Pr), isobutyl (i-Bu), *tert*-butyl (*t*-Bu), *sec*-butyl (*s*-Bu), isopentyl, neopentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentenyl, cyclohexenyl, methylcyclopropyl, ethylcyclohexenyl, butenylcyclopentyl, and the like.

The term "substituted alkyl" or "optionally substituted alkyl" represents an alkyl group as defined above wherein the substitutents are independently selected from halo, cyano, nitro, trihalomethyl, carbamoyl, hydroxy, oxo, $COOR_3$, $CONR_8R_9$,

C_1-C_6alkyl, C_1-C_6alkyloxy, aryloxy, arylC_1-C_6alkyloxy, thio, C_1-C_6alkylthio, arylthio, arylC_1-C_6alkylthio, NR_8R_9, C_1-C_6alkylamino, arylamino, arylC_1-C_6alkylamino, di(arylC_1-C_6alkyl)amino, C_1-C_6alkylcarbonyl, arylC_1-C_6-alkylcarbonyl, C_1-C_6alkylcarboxy, arylcarboxy, arylC_1-C_6alkylcarboxy, C_1-C_6alkylcarbonylamino, -C_1-C_6alkylaminoCOR$_{12}$, arylC_1-
5   C_6alkylcarbonylamino, tetrahydrofuranyl, morpholinyl, piperazinyl, -CONR$_8$R$_9$, -C_1-C_6alkylCONR$_8$R$_9$, or a saturated or partial saturated cyclic 5, 6 or 7 membered amine, imide or lactam; wherein R_{11} is hydroxy, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkyloxy, aryloxy, arylC_1-C_6alkyloxy and R_3 is defined as above or NR8R9, wherein R_8, R_9 are defined as above.

10   The term "saturated, partially saturated or aromatic cyclic, bicyclic or tricyclic ring system" represents but are not limit to aziridinyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, 2-imidazolinyl, imidazolidinyl, pyrazolyl, 2-pyrazolinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, morpholinyl, piperidinyl, thiomorpholinyl, piperazinyl, indolyl, isoindolyl, 1,2,3,4-tetrahydro-quinolinyl, 1,2,3,4-tetrahydro-isoquinolinyl, 1,2,3,4-tetrahydro-quinoxalinyl, indolinyl, indazolyl, benzimi-
15   dazolyl, benzotriazolyl, purinyl, carbazolyl, acridinyl, phenothiazinyl, phenoxazinyl, iminodibenzyl, iminostilbenyl.

The term "alkyloxy" (e.g. methoxy, ethoxy, propyloxy, allyloxy, cyclohexyloxy) represents an "alkyl" group as defined above having the indicated number of carbon atoms attached through an oxygen bridge.
20   The term "alkyloxyalkyl" represents an "alkyloxy" group attached through an alkyl group as defined above having the indicated number of carbon atoms.

The term "alkyloxyalkyloxy" represents an "alkyloxyalkyl" group attached through an oxygen atom as defined above having the indicated number of carbon atoms.

The term "aryloxy" (e.g. phenoxy, naphthyloxy and the like) represents an aryl group
25   as defined below attached through an oxygen bridge.

The term "arylalkyloxy" (e.g. phenethyloxy, naphthylmethyloxy and the like) represents an "arylalkyl" group as defined below attached through an oxygen bridge.

The term "arylalkyloxyalkyl" represents an "arylalkyloxy" group as defined above attached through an "alkyl" group defined above having the indicated number of carbon atoms.
30   The term "arylthio" (e.g. phenylthio, naphthylthio and the like) represents an "aryl" group as defined below attached through an sulfur bridge.

The term "alkyloxycarbonyl" (e.g. methylformiat, ethylformiat and the like) represents an "alkyloxy" group as defined above attached through a carbonyl group.

The term "aryloxycarbonyl" (e.g. phenylformiat, 2-thiazolylformiat and the like)
35   represents an "aryloxy" group as defined above attached through a carbonyl group.

The term "arylalkyloxycarbonyl" (e.g. benzylformiat, phenyletylformiat and the like) represents an "arylalkyloxy" group as defined above attached through a carbonyl group.

The term "alkyloxycarbonylalkyl" represents an "alkyloxycarbonyl" group as defined above attached through an "alkyl" group as defined above having the indicated number of

5   carbon atoms.

The term "arylalkyloxycarbonylalkyl" represents an "arylalkyloxycarbonyl" group as defined above attached through an "alkyl" group as defined above having the indicated number of carbon atoms.

The term "alkylthio" (e.g. methylthio, ethylthio, propylthio, cyclohexenylthio and the

10 like) represents an "alkyl" group as defined above having the indicated number of carbon atoms attached through a sulfur bridge.

The term "arylalkylthio" (e.g. phenylmethylthio, phenylethylthio, and the like) represents an "arylalkyl" group as defined above having the indicated number of carbon atoms attached through a sulfur bridge.

15 The term "alkylthioalkyl" represents an "alkylthio" group attached through an alkyl group as defined above having the indicated number of carbon atoms.

The term "arylalkylthioalkyl" represents an "arylalkylthio" group attached through an alkyl group as defined above having the indicated number of carbon atoms.

The term "alkylamino" (e.g. methylamino, diethylamino, butylamino, N-propyl-N-

20 hexylamino, (2-cyclopentyl)propylamino, hexenylamino, pyrrolidinyl, piperidinyl and the like) represents one or two "alkyl" groups as defined above having the indicated number of carbon atoms attached through an amine bridge. The two alkyl groups may be taken together with the nitrogen to which they are attached forming a saturated, partially saturated or aromatic cyclic, bicyclic or tricyclic ring system containing 3 to 14 carbon atoms and 0 to 3 additional

25 heteroatoms selected from nitrogen, oxygen or sulfur, the ring system can optionally be substituted with at least one C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, oxo, C_1-C_6alkyloxy, C_1-C_6alkyloxyC_1-C_6alkyl, NR8R9, C_1-C_6alkylaminoC_1-C_6alkyl substituent wherein the alkyl and aryl groups are optionally substituted as defined in the definition section and R_8 and R_9 are defined as above.

30 The term "arylalkylamino" (e.g. benzylamino, diphenylethylamino and the like) represents one or two "arylalkyl" groups as defined above having the indicated number of carbon atoms attached through an amine bridge. The two "arylalkyl" groups may be taken together with the nitrogen to which they are attached forming a saturated, partially saturated or aromatic cyclic, bicyclic or tricyclic ring system containing 3 to 14 carbon atoms and 0 to 3 addi-

35 tional heteroatoms selected from nitrogen, oxygen or sulfur, the ring system can optionally be substituted with at least one C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, oxo, C_1-C_6alkyloxy, C_1-

C_6alkyloxyC_1-C_6alkyl, NR_8R_9, C_1-C_6alkylaminoC_1-C_6alkyl substituent wherein the alkyl and aryl groups are optionally substituted as defined in the definition section and R_8 and R_9 are defined as above.

The term "alkylaminoalkyl" represents an "alkylamino" group attached through an al-
5   kyl group as defined above having the indicated number of carbon atoms.

The term "arylalkylaminoalkyl" represents an "arylalkylamino" group attached through an alkyl group as defined above having the indicated number of carbon atoms.

The term "arylamino" represents an "aryl" group as defined below attached through an amino group.

10   The term "arylaminoalkyl" represents an "arylamino" group attached through an alkyl group as defined above having the indicated number of carbon atoms.

The term "arylalkyl" (e.g. benzyl, phenylethyl) represents an "aryl" group as defined below attached through an alkyl having the indicated number of carbon atoms or substituted alkyl group as defined above.

15   The term "alkylcarbonyl" (e.g. cyclooctylcarbonyl, pentylcarbonyl, 3-hexenylcarbonyl) represents an "alkyl" group as defined above having the indicated number of carbon atoms attached through a carbonyl group.

The term "arylcarbonyl" (benzoyl) represents an "aryl" group as defined above attached through a carbonyl group.

20

The ter m "arylalkylcarbonyl" (e.g. phenylcyclopropylcarbonyl, phenylethylcarbonyl and the like) represents an "arylalkyl" group as defined above having the indicated number of carbon atoms attached through a carbonyl group.

The term "alkylcarbonylalkyl" represents an "alkylcarbonyl" group attached through an
25   "alkyl" group as defined above having the indicated number of carbon atoms.

The term "arylalkylcarbonylalkyl" represents an "arylalkylcarbonyl" group attached through an alkyl group as defined above having the indicated number of carbon atoms.

The term "arylcarbonylamino" represents an "arylcarbonyl" group as defined above attached through an amino group.

30   The term "arylcarbonylaminoalkyl" represents an "arylcarbonylamino" group attached through an alkyl group as defined above having the indicated number of carbon atoms.

The term "alkylcarboxy" (e.g. heptylcarboxy, cyclopropylcarboxy, 3-pentenylcarboxy) represents an "alkylcarbonyl" group as defined above wherein the carbonyl is in turn attached through an oxygen bridge.

35   The term "arylcarboxyalkyl" (e.g. phenylcarboxymethyl) represents an

"arylcarbonyl" group defined above wherein the carbonyl is in turn attached through an oxygen bridge to an alkyl chain having the indicated number of carbon atoms.

The term "arylalkylcarboxy" (e.g. benzylcarboxy, phenylcyclopropylcarboxy and the like) represents an "arylalkylcarbonyl" group as defined above wherein the carbonyl is in turn

5   attached through an oxygen bridge.

The term "alkylcarboxyalkyl" represents an "alkylcarboxy" group attached through an "alkyl" group as defined above having the indicated number of carbon atoms.

The term "arylalkylcarboxyalkyl" represents an "arylalkylcarboxy" group attached through an "alkyl" group as defined above having the indicated number of carbon atoms.

10   The term "alkylcarbonylamino" (e.g. hexylcarbonylamino, cyclopentylcarbonyl-aminomethyl, methylcarbonylaminophenyl) represents an "alkylcarbonyl" group as defined above wherein the carbonyl is in turn attached through the nitrogen atom of an amino group. The nitrogen atom may itself be substituted with an alkyl or aryl group.

The term "arylalkylcarbonylamino" (e.g. benzylcarbonylamino and the like) represents

15   an "arylalkylcarbonyl" group as defined above wherein the carbonyl is in turn attached through the nitrogen atom of an amino group. The nitrogen atom may itself be substituted with an alkyl or aryl group.

The term "alkylcarbonylaminoalkyl" represents an "alkylcarbonylamino" group attached through an "alkyl" group as defined above having the indicated number of carbon at-

20   oms. The nitrogen atom may itself be substituted with an alkyl or aryl group.

The term "arylalkylcarbonylaminoalkyl" represents an "arylalkylcarbonylamino" group attached through an "alkyl" group as defined above having the indicated number of carbon atoms. The nitrogen atom may itself be substituted with an alkyl or aryl group.

The term "alkylcarbonylaminoalkylcarbonyl" represents an alkylcarbonylaminoalkyl

25   group attached through a carbonyl group. The nitrogen atom may be further substituted with an "alkyl" or "aryl" group.

The term "aryl" represents an unsubstituted, monocyclic, polycyclic, biaryl and heterocyclic aromatic groups covalently attached at any ring position capable of forming a stable covalent bond, certain preferred points of attachment being apparent to those skilled in the

30   art (e.g., 3-indolyl, 4(5)-imidazolyl).

The definition of aryl includes but is not limited to phenyl, biphenyl, indenyl, fluorenyl, naphthyl (1-naphthyl, 2-naphthyl), pyrrolyl (2-pyrrolyl), pyrazolyl (3-pyrazolyl), imidazolyl (1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), triazolyl (1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl 1,2,3-triazol-4-yl, 1,2,4-triazol-3-yl), oxazolyl (2-oxazolyl, 4-oxazolyl, 5-oxazolyl), isoxazolyl

35   (3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), thiazolyl (2-thiazolyl, 4-thiazolyl, 5-thiazolyl), thiophenyl (2-thiophenyl, 3-thiophenyl, 4-thiophenyl, 5-thiophenyl), furanyl (2-furanyl, 3-furanyl,

4-furanyl, 5-furanyl), pyridyl (2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl), 5-tetrazolyl, pyrimidinyl
(2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl), pyrazinyl, pyridazinyl (3-pyridazinyl,
4-pyridazinyl, 5-pyridazinyl), quinolyl (2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl,
7-quinolyl, 8-quinolyl), isoquinolyl (1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 6-

5   isoquinolyl, 7-isoquinolyl, 8-isoquinolyl), benzo[b]furanyl (2-benzo[b]furanyl, 3-
benzo[b]furanyl, 4-benzo[b]furanyl, 5-benzo[b]furanyl, 6-benzo[b]furanyl, 7-benzo[b]furanyl),
2,3-dihydro-benzo[b]furanyl (2-(2,3-dihydro-benzo[b]furanyl), 3-(2,3-dihydro-benzo[b]furanyl),
4-(2,3-dihydro-benzo[b]furanyl), 5-(2,3-dihydro-benzo-[b]furanyl), 6-(2,3-dihydro-benzo-
[b]furanyl), 7-(2,3-dihydro-benzo[b]furanyl)), benzo[b]thiophenyl (2-benzo[b]thiophenyl, 3-

10 benzo[b]thiophenyl, 4-benzo[b]thiophenyl, 5-benzo[b]thiophenyl, 6-benzo[b]thiophenyl, 7-
benzo[b]thiophenyl), 2,3-dihydro-benzo[b]-thiophenyl (2-(2,3-dihydro-benzo[b]thiophenyl), 3-
(2,3-dihydro-benzo[b]-thiophenyl), 4-(2,3-dihydro-benzo[b]thiophenyl), 5-(2,3-dihydro-
benzo[b]-thiophenyl), 6-(2,3-dihydro-benzo[b]thiophenyl), 7-(2,3-dihydro-benzo[b]-
thiophenyl)), 4,5,6,7-tetrahydro-benzo[b]thiophenyl (2-(4,5,6,7-tetrahydro-benzo-

15 [b]thiophenyl), 3-(4,5,6,7-tetrahydro-benzo-[b]thiophenyl), 4-(4,5,6,7-tetrahydro-
benzo[b]thiophenyl), 5-(4,5,6,7-tetrahydro-benzo-[b]thiophenyl), 6-(4,5,6,7-tetrahydro-benzo-
[b]thiophenyl), 7-(4,5,6,7-tetrahydro-benzo[b]thiophenyl)), 4,5,6,7-tetrahydro-thieno[2,3-
c]pyridyl (4-(4,5,6,7-tetrahydro-thieno[2,3-c]pyridyl), 5-4,5,6,7-tetrahydro-thieno[2,3-c]pyridyl),
6-(4,5,6,7-tetrahydro-thieno[2,3-c]pyridyl), 7-(4,5,6,7-tetrahydro-thieno[2,3-c]pyridyl)), indolyl

20 (1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, 7-indolyl), isoindolyl (1-isoindolyl,
2-isoindolyl, 3-isoindolyl, 4-isoindolyl, 5-isoindolyl, 6-isoindolyl, 7-isoindolyl), 1,3-dihydro-
isoindolyl (1-(1,3-dihydro-isoindolyl), 2-(1,3-dihydro-isoindolyl), 3-(1,3-dihydro-isoindolyl), 4-
(1,3-dihydro-isoindolyl), 5-(1,3-dihydro-isoindolyl), 6-(1,3-dihydro-isoindolyl), 7-(1,3-dihydro-
isoindolyl)), indazole (1-indazolyl, 3-indazolyl, 4-indazolyl, 5-indazolyl, 6-indazolyl, 7-

25 indazolyl), benzimidazolyl (1-benzimidazolyl, 2-benzimidazolyl, 4-benzimidazolyl, 5-
benzimidazolyl, 6-benzimidazolyl, 7-benzimidazolyl, 8-benzimidazolyl), benzoxazolyl (1-
benz-oxazolyl, 2-benzoxazolyl), benzothiazolyl (1-benzothiazolyl, 2-benzo-thiazolyl, 4-
benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, 7-benzothiazolyl), carbazolyl (1-
carbazolyl, 2-carbazolyl, 3-carbazolyl, 4-carbazolyl), 5H-dibenz[b,f]azepine (5H-

30 dibenz[b,f]azepin-1-yl, 5H-dibenz-[b,f]azepine-2-yl, 5H-dibenz[b,f]azepine-3-yl, 5H-dibenz-
[b,f]azepine-4-yl, 5H-dibenz[b,f]-azepine-5-yl), 10,11-dihydro-5H-dibenz[b,f]azepine (10,11-
dihydro-5H-dibenz[b,f]azepine-1-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-2-yl, 10,11-dihydro-
5H-dibenz[b,f]azepine-3-yl, 10,11-dihydro-5H-dibenz-[b,f]azepine-4-yl, 10,11-dihydro-5H-
dibenz[b,f]azepine-5-yl), piperidinyl (2-piperidinyl, 3-piperidinyl, 4-piperidinyl), pyrrolidinyl (1-

35 pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl), phenylpyridyl (2-phenyl-pyridyl, 3-phenyl-pyridyl, 4-
phenylpyridyl), phenylpyrimidinyl (2-phenylpyrimidinyl, 4-phenyl-pyrimidinyl, 5-

phenylpyrimidinyl, 6-phenylpyrimidinyl), phenylpyrazinyl, phenylpyridazinyl (3-phenylpyridazinyl, 4-phenylpyridazinyl, 5-phenyl-pyridazinyl).

The term "optionally substituted aryl" represents an mono-, di- or trisubstituted aryl as defined above wherein the substituents are independently selected from the group consisting of halo, nitro, cyano, trihalomethyl, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, COOR$_3$, CONR$_8$R$_9$, C_1-C_6alkyloxy, C_1-C_6alkyloxyC_1-C_6alkyl, aryloxy, arylC_1-C_6alkyloxy, arylC_1-C_6alkyl-oxyC_1-C_6alkyl, thio, C_1-C_6alkylthio, C_1-C_6alkylthioC_1-C_6alkyl, arylthio, arylC_1-C_6alkylthio, arylC_1-C_6alkylthioC_1-C_6alkyl, NR$_8$R$_9$, C_1-C_6-alkylamino, C_1-C_6alkyl-aminoC_1-C_6alkyl, arylamino, arylC_1-C_6alkylamino, arylC_1-C_6alkyl-aminoC_1-C_6alkyl, di(arylC_1-C_6alkyl)aminoC_1-C_6alkyl, C_1-C_6alkylcarbonyl, C_1-C_6alkyl-carbonylC_1-C_6alkyl, arylC_1-C_6alkylcarbonyl, arylC_1-C_6alkylcarbonylC_1-C_6alkyl, C_1-C_6alkyl-carboxy, C_1-C_6alkylcarboxyC_1-C_6alkyl, arylC_1-C_6alkylcarboxy, arylC_1-C_6alkyl-carboxyC_1-C_6alkyl, carboxyC_1-C_6-alkyloxy, C_1-C_6alkylcarbonylamino, C_1-C_6alkyl-carbonylaminoC_1-C_6alkyl, -carbonylNR$_7$$C_1$-$C_6$alkylCOR$_{11}$, aryl$C_1$-$C_6$alkylcarbonyl-amino, arylC_1-C_6-alkylcarbonylaminoC_1-C_6alkyl,-CONR$_8$R$_9$, or -C_1-C_6alkylCONR$_8$R$_9$; wherein R$_3$, R$_8$, R$_9$, and R$_{11}$ are defined as above and the alkyl and aryl groups are optionally substituted as defined in the definition section;

The term "arylcarbonyl" (e.g. 2-thiophenylcarbonyl, 3-methoxy-anthrylcarbonyl, oxazolylcarbonyl) represents an "aryl" group as defined above attached through a carbonyl group.

The term "arylalkylcarbonyl" (e.g. (2,3-dimethoxyphenyl)propylcarbonyl, (2-chloronaphthyl)pentenylcarbonyl, imidazolylcyclopentylcarbonyl) represents an "arylalkyl" group as defined above wherein the "alkyl" group is in turn attached through a carbonyl.

The compounds of the present invention have asymmetric centers and may occur as racemates, racemic mixtures, and as individual enantiomers or diastereoisomers, with all isomeric forms being included in the present invention as well as mixtures thereof.
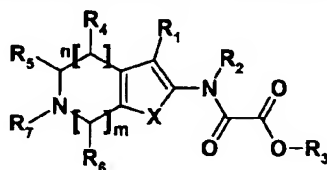
Pharmaceutically acceptable salts of the Compounds of Formula 1, where a basic or acidic group is present in the structure, are also included within the scope of this invention. When an acidic substituent is present, such as -COOH, 5-tetrazolyl or -P(O)(OH)$_2$, there can be formed the ammonium, morpholinium, sodium, potassium, barium, calcium salt, and the like, for use as the dosage form. When a basic group is present, such as amino or a basic heteroaryl radical, such as pyridyl, an acidic salt, such as hydrochloride, hydrobromide, phosphate, sulfate, trifluoroacetate, trichloroacetate, acetate, oxalate, maleate, pyruvate, malonate, succinate, citrate, tartarate, fumarate, mandelate, benzoate, cinnamate, methanesulfonate, ethane sulfonate, picrate and the like, and include acids related to the pharmaceuti-

cally acceptable salts listed in Journal of Pharmaceutical Science, 66, 2 (1977) and incorporated herein by reference, can be used as the dosage form.

Also, in the case of the -COOH or -P(O)(OH)$_2$ being present, pharmaceutically acceptable esters can be employed, e.g., methyl, *tert*-butyl, pivaloyloxymethyl, and the like, and those esters known in the art for modifying solubility or hydrolysis characteristics for use as sustained release or prodrug formulations.

In addition, some of the compounds of the present invention may form solvates with water or common organic solvents. Such solvates are encompassed within the scope of the invention.

The term "therapeutically effective amount" shall mean that amount of drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal, or human that is being sought by a researcher, veterinarian, medical doctor or other.

In a preferred embodiment, the present invention is concerned with compounds of Formula I

Formula 1

wherein

n is 0, 1 or 2;

m is 1 or 2;

X is S or O;

R$_1$ is hydrogen or COOR$_3$, or R$_1$ is selected from the group consisting of the following 5-membered heterocycles:

R_2 is hydrogen, C_1-C_6alkyl, hydroxy or NR_8R_9;

R_3 is hydrogen, C_1-C_6alkyl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyloxyC_1-C_6alkyl or C_1-C_6alkylcarbonyloxyarylC_1-C_6alkyl;

R_4, R_5 and R_6 are independently hydrogen, trihalomethyl, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, oxo, carboxy, carboxyC_1-C_6alkyl, C_1-C_6alkyloxy-carbonyl, aryloxycarbonyl, arylC_1-C_6alkyloxycarbonyl, C_1-C_6alkyloxy, C_1-C_6alkyloxyC_1-C_6alkyl, aryloxy, arylC_1-C_6alkyloxy, arylC_1-C_6alkyloxyC_1-C_6alkyl, thio, C_1-C_6alkyl-thio, C_1-C_6alkylthioC_1-C_6alkyl, arylthio, arylC_1-C_6alkylthio, arylC_1-C_6alkylthioC_1-C_6alkyl, NR_8R_9, C_1-C_6alkylaminoC_1-C_6alkyl, arylC_1-C_6alkylaminoC_1-C_6alkyl, di(arylC_1-C_6alkyl)aminoC_1-C_6alkyl, C_1-C_6alkylcarbonyl, C_1-C_6alkylcarbonylC_1-C_6alkyl, arylC_1-C_6alkylcarbonyl, arylC_1-C_6alkylcarbonylC_1-C_6alkyl, C_1-C_6alkyl-carboxy, C_1-C_6alkylcarboxyC_1-C_6-alkyl, arylcarboxy, arylcarboxyC_1-C_6alkyl, arylC_1-C_6alkylcarboxy, arylC_1-C_6alkylcarboxyC_1-C_6alkyl, C_1-C_6alkylcarbonylamino, C_1-C_6alkylcarbonylaminoC_1-C_6alkyl, -carbonylNR_8C_1-C_6alkylCOR_{12}, arylC_1-C_6alkylcarbonylamino, arylC_1-C_6alkylcarbonylaminoC_1-C_6alkyl, $CONR_8R_9$, or C_1-C_6alkyl$CONR_8R_9$ wherein the alkyl and aryl groups are optionally substituted and R_{12} is NR_8R_9, or C_1-C_6alkylNR_8R_9;

R_7 is hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, C_1-C_6alkyloxocarbonyl, arylcarbonyl, aryloxocarbonyl, arylC_1-C_6alkylcarbonyl, arylC_1-C_6alkyloxocarbonyl, C_1-C_6alkylcarboxy, arylC_1-C_6alkylcarboxy, $R_{10}R_{11}$NcarbonylC_1-C_6alkyl wherein R_{10} and R_{11} are independently selected from hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, arylcarbonyl, arylC_1-C_6alkylcarbonyl, C_1-C_6alkylcarboxy or arylC_1-C_6alkylcarboxy; wherein the alkyl and aryl groups are optionally substituted;

28

R_8 and R_9 are independently selected from hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, C_1-C_6alkyloxocarbonyl, arylcarbonyl, aryloxocarbonyl, arylC_1-C_6alkylcarbonyl, arylC_1-C_6alkyloxocarbonyl, C_1-C_6alkylcarboxy, arylC_1-C_6alkylcarboxy, $R_{10}R_{11}$NcarbonylC_1-C_6alkyl wherein the alkyl and aryl groups are optionally substituted; or

5 R_8 and R_9 are together with the nitrogen to which they are attached forming a saturated, partially saturated or aromatic cyclic, bicyclic or tricyclic ring system containing from 3 to 14 carbon atoms and from 0 to 3 additional heteroatoms selected from nitrogen, oxygen or sulphur, the ring system can optionally be substituted with at least one C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, oxo, C_1-C_6alkyloxy, arylC_1-C_6alkyloxy, C_1-C_6alkyloxyC_1-C_6alkyl, $NR_{10}R_{11}$ or C_1-

10 C_6alkylaminoC_1-C_6alkyl, wherein R_{10} and R_{11} are independently selected from hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, arylcarbonyl, arylC_1-C_6alkylcarbonyl, C_1-C_6alkylcarboxy or arylC_1-C_6alkylcarboxy; wherein the alkyl and aryl groups are optionally substituted; or

R_8 and R_9 are independently a saturated or partial saturated cyclic 5, 6 or 7 membered ami-

15 ne, imide or lactam;

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form.

In another preferred embodiment, the present invention is concerned with compounds

20 wherein X is sulphur.

In another preferred embodiment, the present invention is concerned with compounds wherein R_1 is $COOR_3$ and R_2 is hydrogen; wherein R_3 is defined as above.

In another preferred embodiment, the present invention is concerned with compounds wherein n and m are 1.

25 In another preferred embodiment, the present invention is concerned with compounds wherein R_5 is C_1-C_6alkylNR_8R_9$.

In another preferred embodiment, the present invention is concerned with compounds wherein R_4 and R_6 are hydrogen.

In another preferred embodiment, the present invention is concerned with compounds

30 wherein R_1 is 5-tetrazolyl, R_2 is hydrogen, and R_5 is C_1-C_6alkylNR_8R_9$.

In another preferred embodiment, the present invention is concerned with compounds wherein R_6 is C_1-C_6alkylNR_8R_9$.

In another preferred embodiment, the present invention is concerned with compounds wherein R_4 and R_5 are hydrogen.

35 In another preferred embodiment, the present invention is concerned with compounds wherein R_1 is 5-tetrazolyl, R_2 is hydrogen, and R_6 is C_1-C_6alkylNR_8R_9$.

In another preferred embodiment, the present invention is concerned with compounds wherein R_5 and R_6 are C_1-C_6alkylNR$_8$R$_9$.

In another preferred embodiment, the present invention is concerned with compounds wherein R_1 is COOR$_3$ and R_2 is hydrogen; wherein R_3 is defined as above.

In another preferred embodiment, the present invention is concerned with compounds wherein R_1 is 5-tetrazolyl.

In another preferred embodiment, the present invention is concerned with compounds wherein R_8 and R_9 are together with the nitrogen to which they are attached forming a partially saturated bicyclic ring system containing 8 carbon atoms, the ring system being optionally substituted with two oxo groups.

In another preferred embodiment, the present invention is concerned with compounds wherein the ring system is isoindolyl.

In another preferred embodiment, the present invention is concerned with compounds wherein R_7 is C_1-C_6alkyloxo-carbonyl.

In another preferred embodiment, the present invention is concerned with compounds wherein R_8 and R_9 are together with the nitrogen to which they are attached forming a partially saturated bicyclic ring system containing 8 carbon atoms, the ring system being optionally substituted with two oxo groups.

In another preferred embodiment, the present invention is concerned with compounds wherein the ring system is isoindolyl.

In another preferred embodiment, the present invention is concerned with compounds wherein R_8 and R_9 are together with the nitrogen to which they are attached forming a partially saturated bicyclic ring system containing 7 carbon atoms and one sulfur atom, the ring system being optionally substituted with three oxo groups.

In another preferred embodiment, the present invention is concerned with compounds wherein the ring system is 2,3-dihydro-benzo[d]iosthiazolyl.

In another preferred embodiment, the present invention is concerned with compounds wherein R_8 and R_9 are together with the nitrogen to which they are attached forming a partially saturated bicyclic ring system containing 7 carbon atoms and one sulfur atom, the ring system being optionally substituted with two oxo groups.

In another preferred embodiment, the present invention is concerned with compounds wherein the ring system is 2,3-dihydro-benzo[d]iosthiazolyl.

In another preferred embodiment, the present invention is concerned with compounds wherein R_7 is C_1-C_6alkyloxo-carbonyl.

In another preferred embodiment, the present invention is concerned with compounds wherein R_8 and R_9 are together with the nitrogen to which they are attached forming a par-

tially saturated bicyclic ring system containing 8 carbon atoms, the ring system being option-
ally substituted with one oxo group.

In another preferred embodiment, the present invention is concerned with compounds
wherein the ring system is optionally substituted isoindolyl.

In another preferred embodiment, the present invention is concerned with compounds
wherein the ring system is optionally substituted 1-oxo-1,3-dihydro-isoindolyl.

In another preferred embodiment, the present invention is concerned with com-
pounds wherein R_7 is C_1-C_6alkyloxo-carbonyl.

In another preferred embodiment, the present invention is concerned with compounds
wherein R_5 and R_6 are C_1-C_6alkylNR$_8$R$_9$.

In another preferred embodiment, the present invention is concerned with compounds
of Formula I wherein R_5 is 1,3-dihydro-isoindol, substituted with 1 or 2 oxo groups at the atom
positions adjacent to the nitrogen atom and optionally substituted with hydroxy, C_{1-6}-alkyloxy,
arylC_{1-6}-alkyloxy or C_{1-6}-alkylcarboxy, and wherein R_7 is hydrogen, alkyl, alkyloxycarbonyl,
arylalkyl or aryl wherein aryl is optionally substituted with methoxy.

In another preferred embodiment, the present invention is concerned with compounds
of Formula I wherein R_5 is 1,1,3-trioxo-1,2-dihydro-1H-benzo[d]isothiazol-2-yl and wherein R_7
is hydrogen or arylalkyl.

In another preferred embodiment, the present invention is concerned with compounds
of Formula I wherein R_5 or R_6 is arylaminoalkyl, wherein aryl is 1,1-dioxo-1,2-dihydro-1H-
benzo[d]isothiazol-3-yl.

In another preferred embodiment, the present invention is concerned with compounds
of Formula I wherein R_5 or R_6 is arylcarbonylaminoalkyl, wherein aryl is phenyl, indol-3-yl,
indol-2-yl, 1,2,3-triazol-4-yl, quinolin-4-yl or naphth-1-yl wherein aryl is optionally substituted,
and wherein R_7 is hydrogen or arylalkyl optionally substituted with methoxy.

In another preferred embodiment, the present invention is concerned with compounds
of Formula I wherein R_5 is arylalkylaminoalkyl wherein aryl is phenyl, dibenzofuranyl, naphth-
2-yl or indo-3-yl, and wherein alkyl and aryl are optionally substituted, and wherein R_7 is hy-
drogen or arylalkyl optionally substituted with methoxy.

In another preferred embodiment, the present invention is concerned with compounds
of Formula I wherein R_6 is alkylNR$_8$R$_9$, wherein R_8 is alkylcarbonyl and R_9 is arylalkyl, whe-
rein aryl is optionally substituted.

In a preferred embodiment of the invention X in formula 1 is sulphur.

In another preferred embodiment of the invention R_1 is COOR$_3$ and R_2 is
hydrogen; wherein R_3 is hydrogen, C_1-C_6alkyl or arylC_1-C_6alkyl.

In a further preferred embodiment of the invention n and m are 1.

In a further preferred embodiment of the invention R_4 and R_6 are both hydrogen and R_5 is C_1-C_6alkylNR$_8$R$_9$ and R_8 and R_9 are together with the nitrogen to which they are attached forming a partially saturated bicyclic ring system containing 8 carbon atoms, the ring system being optionally substituted with two oxo groups.

Most preferred are R_8 and R_9 together with the nitrogen to which they are attached forming an isoindolyl-1,3-dione optionally substituted.

In another preferred embodiment of the invention R_4 and R_5 are both hydrogen and R_6 is C_1-C_6alkylNR$_8$R$_9$ and R_8 and R_9 are together with the nitrogen to which they are attached forming a partially saturated bicyclic ring system containing 8 carbon atoms, the ring system being optionally substituted with three oxo groups.

Most preferred are R_8 and R_9 together with the nitrogen to which they are attached forming an 1,1-dioxo-1,2-dihydro-1H-benzo[d]isothiazolyl-3-one optionally substituted.

In a further preferred embodiment of the invention R_4 and R_5 are both hydrogen and R_6 is C_1-C_6alkylNR$_8$R$_9$ and R_8 and R_9 are together with the nitrogen to which they are attached forming a partially saturated bicyclic ring system containing 8 carbon atoms, the ring system being optionally substituted with two oxo groups.

Most preferred are R_8 and R_9 together with the nitrogen to which they are attached forming an isoindolyl-1,3-dione optionally substituted.

In a further preferred embodiment of the invention R_4 and R_6 are both hydrogen and R_5 is C_1-C_6alkylNR$_8$R$_9$ and R_8 and R_9 are together with the nitrogen to which they are attached forming a partially saturated bicyclic ring system containing 8 carbon atoms, the ring system being optionally substituted with one oxo group.

Most preferred are R_8 and R_9 together with the nitrogen to which they are attached forming an optionally substituted 1-oxo-1,3-dihydro-isoindolyl ring.

In another preferred embodiment of the invention R_4 and R_5 are both hydrogen and R_6 is C_1-C_6alkylNR$_8$R$_9$ and R_8 and R_9 are together with the nitrogen to which they are attached forming a partially saturated bicyclic ring system containing 8 carbon atoms, the ring system being optionally substituted with one oxo group.

Most preferred are R_8 and R_9 together with the nitrogen to which they are attached forming an optionally substituted 1-oxo-1,3-dihydro-isoindolyl ring.

In a further preferred embodiment of the invention R_7 is C_1-C_6alkyloxocarbonyl.

The following compounds are preferred:

5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid 6-ethyl ester;

32

5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

(L)-5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5   7-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(4-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-5-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-

10   c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-7-(1,1,3-trioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-(1,1-Dioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

15   5-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

or a pharmaceutically acceptable salt thereof.

20   The following compounds are also preferred:

5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid 6-ethyl ester;

5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

25   (S)-5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(4-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-

30   thieno[2,3-c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-5-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(4-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

35   5-(4-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-methyl-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

33

5-((1,1-Dioxo-1H-benzo[d]isothiazol-3-ylamino)-methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-((1,1-Dioxo-1H-benzo[d]isothiazol-3-ylamino)-methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5   5-(7-Methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(7-Benzyloxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-

10   thieno[2,3-c]pyridine-3-carboxylic acid;

5-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

15   7-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-

20   tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(S)-(7-Methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(R)-(7-Methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

25   5-(4-Benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(6-Methoxy-4-methoxycarbonyl-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-5-(1,1,3-trioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-

30   5H-thieno[2,3-c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-7-(1,1,3-trioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyridine-3-carboxylic acid;

7-Carbamoyl-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-5-(2-oxo-tetrahydro-thiophen-3-ylcarbamoyl)-4,5,6,7-tetrahydro-thieno[2,3-

35   c]pyridine-3-carboxylic acid;

34

2-(Oxalyl-amino)-5-phenylcarbamoyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-7-phenylcarbamoyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5

or a pharmaceutically acceptable salt thereof.

The following compounds are also preferred:

10   5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid 6-ethyl ester;

5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(S)-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-

15   thieno[2,3-c]pyridine-3-carboxylic acid;

7-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(4-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

20   7-(4-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-5-(S)-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(4-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-

25   thieno[2,3-c]pyridine-3-carboxylic acid;

5-(4-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-methyl-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-((1,1-Dioxo-1H-benzo[d]isothiazol-3-ylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

30   7-((1,1-Dioxo-1H-benzo[d]isothiazol-3-ylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(7-Methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-

35   thieno[2,3-c]pyridine-3-carboxylic acid;

5-(7-Benzyloxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-
thieno[2,3-c]pyridine-3-carboxylic acid;

5-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-
4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5   5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-
thieno[2,3-c]pyridine-3-carboxylic acid;

7-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-

10   4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-(((5-Benzyloxy-1H-indole-2-carbonyl)amino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-
4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

15   7-(((6-Bromo-2-p-tolyl-quinoline-4-carbonyl)amino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-
amino)- 4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

6-(4-Methoxy-benzyl)-7-(((5-methyl-2-phenyl-2H-[1,2,3]triazole-4-carbonyl)amino)methyl)-2-
(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-(((1H-Indole-3-carbonyl)amino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-

20   tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-((4-Ethoxy-2-hydroxy-benzoylamino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-
4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-((4-Benzoylamino-benzoylamino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

25   7-(((Biphenyl-4-carbonyl)-amino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-(((1H-Indole-2-carbonyl)amino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-((3-Biphenyl-4-yl-acryloylamino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-

30   tetrahydro-thieno[2,3-c)pyridine-3-carboxylic acid;

6-(4-Methoxy-benzyl)-7-(((5-methoxy-1H-indole-2-carbonyl)amino)methyl)-2-(oxalyl-amino)-
4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-((4-Benzyl-benzoylamino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

35   6-(4-Methoxy-benzyl)-7-(((naphthalene-1-carbonyl)amino)methyl)-2-(oxalyl-amino)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

6-(4-Methoxy-benzyl)-5-((2-naphthalen-2-yl-ethylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-((2-Benzo[1,3]dioxol-5-yl-acetylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5   5-((2-Dibenzofuran-2-yl-ethyl)amino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

6-(4-Methoxy-benzyl)-5-((2-(5-methoxy-2-methyl-1*H*-indol-3-yl)-acetylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

<u>5-((2-(1*H*-Indol-3-yl)-2-oxo-acetylamino)methyl)-2-(Oxalyl-amino)-4,5,6,7-tetrahydro-</u>

10 <u>thieno[2,3-c]pyridine-3-carboxylic acid;</u>

5-(*R*)-(7-Methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(*S*)-(7-Methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

15 5-(*S*)-(4-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-5-(*S*)-((4-phenoxy-benzylamino)methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(*S*)-((4-Acetylamino-benzylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-

20 c]pyridine-3-carboxylic acid;

7-(*S*)-((Acetyl-(4-phenoxy-benzyl)amino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-(*S*)-((Acetyl-benzyl-amino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

25 5-(*S*)-((1,1-Dioxo-1*H*-benzo[d]isothiazol-3-ylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(4-Benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(6-Methoxy-4-methoxycarbonyl-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-

30 4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-5-(1,1,3-trioxo-1,3-dihydro-1*H*-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-5*H*-thieno[2,3-c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-7-(1,1,3-trioxo-1,3-dihydro-1*H*-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-5*H*-thieno[2,3-c]pyridine-3-carboxylic acid;

35 7-(*R*)-Carbamoyl-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-5-(S)-(2-oxo-tetrahydro-thiophen-3-ylcarbamoyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-5-(S)-phenylcarbamoyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5   2-(Oxalyl-amino)-7-(R)-phenylcarbamoyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(R),7-(R)-Bis-benzyloxymethyl-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

6-Benzyl-2-(oxalyl-amino)-5-(1,1,3-trioxo-1,3-dihydro-1,6-benzo[d]isothiazol-2-ylmethyl)-

10   4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form, or prodrug thereof.

15

PHARMACOLOGICAL METHODS

The compounds are evaluated for biological activity with a truncated form of PTP1B (corresponding to the first 321 amino acids), which was expressed in E. coli and purified to apparent homogeneity using published procedures well-known to those skilled in the art. The en-

20   zyme reactions are carried out using standard conditions essentially as described by Burke et al. (*Biochemistry* 35; 15989-15996 (1996)). The assay conditions are as follows. Appropriate concentrations of the compounds of the invention are added to the reaction mixtures containing different concentrations of the substrate, p-nitrophenyl phosphate (range: 0.16 to 10 mM - final assay concentration). The buffer used was 50 mM HEPES pH 7.0, 100 mM so-

25   dium chloride, 0.1 % (w/v) bovine serum albumin, 5 mM glutathione, and 1 mM EDTA. The reaction was started by addition of the enzyme and carried out in microtiter plates at 25 °C for 60 minutes. The reactions are stopped by addition of NaOH. The enzyme activity was determined by measurement of the absorbance at 405 nm with appropriate corrections for absorbance at 405 nm of the compounds and p-nitrophenyl phosphate. The data are analyzed

30   using nonlinear regression fit to classical Michaelis Menten enzyme kinetic models. Inhibition is expressed as K_i values in nM. The results of representative experiments are shown in Table 1.

Table 1

Inhibition of classical PTP1B by compounds
of the invention

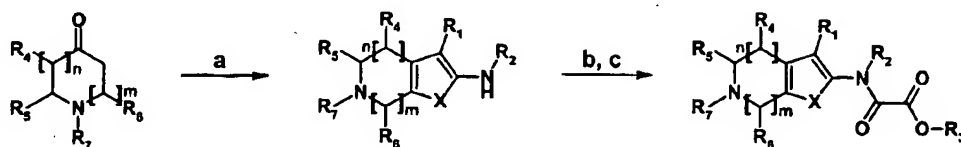| Example no.	PTP1B K_i values (nM)
8	250
10	270
11	240
12	570
36	830
42	220
46	300

5   **Analysis for blood glucose lowering effects**

The compounds of the invention are tested for blood glucose lowering effects in diabetic,
obese female ob/ob mice. The mice are of similar age and body weights and they are ran-
domized into groups of ten mice. They have free access to food and water during the expe-
riment. The compounds are administered by either by gavage, subcutaneous, intravenous or
10 intraperitoneal injections. The control group receives the same volume of vehicle as the mice
that receive the compounds. Non-limiting examples of dose-range: 0.1, 0.3, 1.0, 3.0,10, 30,
100 mg per kg body weight. The blood glucose levels are measured two times before admi-
nistration of the compounds of the invention and vehicle (to the control group). After admini-
stration of the compound, the blood glucose levels are measured at the following time points:
15 1, 2, 4, 6, and 8 hours. A positive response is defined either as (i) a more than 25 percent
reduction in blood glucose levels in the group receiving the compound of the invention com-
pared to the group receiving the vehicle at any time point or (ii) statistically significant (i.e.
$p < 0.05$) reduction in the area under the blood glucose curve during the whole period (i.e. 8
hrs) in the group treated with the compounds of the invention compared to the group recei-
20 ving the vehicle.

Compounds that show positive response can be used as development candidates
and used for treatment of human diseases such as diabetes and obesity.

25

THE SYNTHESIS OF THE COMPOUNDS

In accordance with one aspect of the invention, the compounds of the invention are prepared as illustrated in the following reaction scheme:
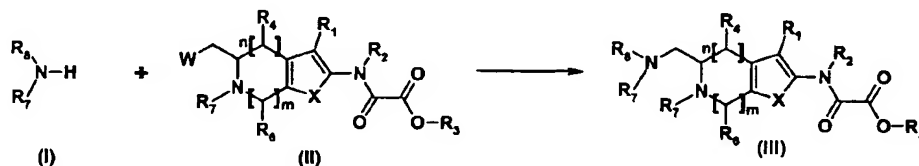
5 **Method A**

a) $NCCH_2COOR_3$, sulphur, morpholine or triethylamine, ethanol; b) $R_3OCOCOimidazole$, tet-
10 rahydrofuran; c) 25 % trifluoroacetic acid/dichloromethane; wherein n, m, X, R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are defined above;

When R_4 is hydrogen the reaction step a) in Method A gives a mixture of regioisomers which can be separated by use of column chromatography known to thus skilled in the art.

15

Method B

(I)   (II)   (III)

20 By allowing an amine (I) and a substituted oxalylamide (II) to react under basic conditions (e.g. K_2CO_3, in N,N-dimethylformamide or methylethylketone) or under Mitsunobu conditions (Oyo Mitsunobu, Synthesis, (1981) 1-28) to yield (III) wherein W is OH, OSO_2Me or halo, and n, m, X, R_1, R_2, R_3, R_4, R_6, R_7 and R_8 are defined above.

25 **Method C**

(I)   (II)   (III)

By allowing an amine (I) and a substituted oxalylamide (II) to react under basic conditions (e.g. K_2CO_3, in N,N-dimethylformamide or methylethylketone) or under Mitsunobu conditions (Oyo Mitsunobu, Synthesis, (1981) 1-28) to yield (III) wherein W is OH, OSO_2Me or halo, and n, m, X, R_1, R_2, R_3, R_4, R_5, R_7 and R_8 are defined above.

5   Pharmacological Preparations

In another aspect, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of the general formula I or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or
10   diluent.

The present compounds may also be administered in combination with one or more further pharmacologically active substances eg., selected from antiobesity agents, antidiabetics, antihypertensive agents, agents for the treatment and/or prevention of complications resulting from or associated with diabetes and agents for the treatment and/or prevention of com-
15   plications and disorders resulting from or associated with obesity.

Thus, in a further aspect of the invention the present compounds may be administered in combination with one or more antiobesity agents or appetite regulating agents.

Such agents may be selected from the group consisting of CART (cocaine amphetamine regulated transcript) agonists, NPY (neuropeptide Y) antagonists, MC4 (melanocortin
20   4) agonists, orexin antagonists, TNF (tumor necrosis factor) agonists, CRF (corticotropin releasing factor) agonists, CRF BP (corticotropin releasing factor binding protein) antagonists, urocortin agonists, β3 agonists, MSH (melanocyte-stimulating hormone) agonists, MCH (melanocyte-concentrating hormone) antagonists, CCK (cholecystokinin) agonists, serotonin re-uptake inhibitors, serotonin and noradrenaline re-uptake inhibitors, mixed serotonin and
25   noradrenergic compounds, 5HT (serotonin) agonists, bombesin agonists, galanin antagonists, growth hormone, growth hormone releasing compounds, TRH (thyreotropin releasing hormone) agonists, UCP 2 or 3 (uncoupling protein 2 or 3) modulators, leptin agonists, DA agonists (bromocriptin, doprexin), lipase/amylase inhibitors, PPAR (peroxisome proliferator activated receptor) modulators, RXR (retinoid X receptor) modulators or TR β agonists.
30   In one embodiment of the invention the antiobesity agent is leptin.
In another embodiment the antiobesity agent is dexamphetamine or amphetamine.
In another embodiment the antiobesity agent is fenfluramine or dexfenfluramine.
In still another embodiment the antiobesity agent is sibutramine.
In a further embodiment the antiobesity agent is orlistat.
35   In another embodiment the antiobesity agent is mazindol or phentermine.

Suitable antidiabetics comprise insulin, GLP-1 (glucagon like peptide-1) derivatives such as those disclosed in WO 98/08871 to Novo Nordisk A/S, which is incorporated herein by reference as well as orally active hypoglycaemic agents.

The orally active hypoglycaemic agents preferably comprise sulphonylureas, biguanides, meglitinides, oxadiazolidinediones, thiazolidinediones, glucosidase inhibitors, glucagon antagonists such as those disclosed in WO 99/01423 to Novo Nordisk A/S and Agouron Pharmaceuticals, Inc., GLP-1 agonists, potassium channel openers such as those disclosed in WO 97/26265 and WO 99/03861 to Novo Nordisk A/S which are incorporated herein by reference, insulin sesitizers, DPP-IV (dipeptidyl peptidase-IV) inhibitors, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis and/or glycogenolysis, glucose uptake modulators, compounds modifying the lipid metabolism such as antihyperlipidemic agents and antilipidemic agents as HMG CoA inhibitors (statins), compounds lowering food intake, PPAR and RXR agonists and agents acting on the ATP-dependent potassium channel of the β-cells.

In one embodiment of the invention the present compounds are administered in combination with insulin.

In a further embodiment the present compounds are administered in combination with a sulphonylurea eg. tolbutamide, glibenclamide, glipizide or glicazide.

In another embodiment the present compounds are administered in combination with a biguanide eg. metformin.

In yet another embodiment the present compounds are administered in combination with a meglitinide eg. repaglinide.

In still another embodiment the present compounds are administered in combination with a thiazolidinedione eg. troglitazone, ciglitazone, pioglitazone, rosiglitazone or compounds disclosed in WO 97/41097 such as 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione or a pharmaceutically acceptable salt thereof, preferably the potassium salt.

Furthermore, the present compounds may be administered in combination with the insulin sensitizers disclosed in WO 99/19313 such as (-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or a pharmaceutically acceptable salts thereof, preferably the arginine salt.

In a further embodiment the present compounds are administered in combination with an α-glucosidase inhibitor eg. miglitol or acarbose.

In another embodiment the present compounds are administered in combination with an agent acting on the ATP-dependent potassium channel of the β-cells eg. tolbutamide, glibenclamide, glipizide, glicazide or repaglinide.

Furthermore, the present compounds may be administered in combination with nateglinide.

In still another embodiment the present compounds are administered in combination with an antihyperlipidemic agent or antilipidemic agent eg. cholestyramine, colestipol, clofi-
brate, gemfibrozil, lovastatin, pravastatin, simvastatin, probucol or dextrothyroxine.

In a further embodiment the present compounds are administered in combination with more than one of the above-mentioned compounds eg. in combination with a sulphonylurea and metformin, a sulphonylurea and acarbose, repaglinide and metformin, insulin and a sul-phonylurea, insulin and metformin, insulin, insulin and lovastatin, etc.

Furthermore, the present compounds may be administered in combination with one or more antihypertensive agents. Examples of antihypertensive agents are β-blockers such as alprenolol, atenolol, timolol, pindolol, propranolol and metoprolol, ACE (angiotensin con-verting enzyme) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril and ramipril, calcium channel blockers such as nifedipine, felodipine, nicardipine, isradipine, nimodipine, diltiazem and verapamil, and α-blockers such as doxazosin, urapidil, prazosin and terazosin. Further reference can be made to Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

It should be understood that any suitable combination of the compounds according to the invention with one or more of the above-mentioned compounds and optionally one or more further pharmacologically active substances are considered to be within the scope of the present invention.

For the above indications the dosage will vary depending on the compound of the invention em-ployed, on the mode of administration and on the therapy desired. However, in general, satisfactory results are obtained with a dosage of from about 0.5 mg to about 1000 mg, preferably from about 1 mg to about 500 mg of compounds of the invention, conveniently given from 1 to 5 times daily, optionally in sustained release form. Usually, dosage forms suitable for oral administration comprise from about 0.5 mg to about 1000 mg, preferably from about 1 mg to about 500 mg of the compounds of the invention admixed with a pharmaceutical carrier or diluent. The compounds of the invention may be administered in a pharmaceutically acceptable acid addition salt form or where possible as a metal or a C_{1-6}-alkylammonium salt. Such salt forms exhibit approximately the same order of activity as the free acid forms.

This invention also relates to pharmaceutical compositions comprising a compound of the invention or a pharmaceutically acceptable salt thereof and, usually, such compositions also contain a pharmaceutical carrier or diluent. The compositions containing the compounds of this invention may be prepared by conventional techniques and appear in conventional forms, for example capsules, tablets, solutions or suspensions.

The pharmaceutical carrier employed may be a conventional solid or liquid carrier. Examples of solid carriers are lactose, terra alba, sucrose, talc, gelatine, agar, pectin, acacia, magnesium stearate and stearic acid. Examples of liquid carriers are syrup, peanut oil, olive oil and water.

Similarly, the carrier or diluent may include any time delay material known to the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax.

If a solid carrier for oral administration is used, the preparation can be tabletted, placed in a hard gelatine capsule in powder or pellet form or it can be in the form of a troche or lozenge. The amount of solid carrier will vary widely but will usually be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

Generally, the compounds of this invention are dispensed in unit dosage form comprising 10-200 mg of active ingredient in or together with a pharmaceutically acceptable carrier per unit dosage.

The dosage of the compounds according to this invention is 1-500 mg/day, e.g. about 100 mg per dose, when administered to patients, e.g. humans, as a drug.

A typical tablet that may be prepared by conventional tabletting techniques contains

Core:

Active compound (as free compound   100 mg
or salt thereof)

Colloidal silicon dioxide (Areosil®)   1.5 mg

Cellulose, microcryst. (Avicel®)   70 mg

Modified cellulose gum (Ac-Di-Sol®)   7.5 mg

Magnesium stearate

Coating:

HPMC   approx.   9 mg

ˉMywacett® 9-40 T   approx.   0.9 mg

ˉAcylated monoglyceride used as plasticiser for film coating.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral or parenteral e.g. rectal, transdermal, subcutaneous, intranasal, intramuscular, topical, intravenous, intraurethral, ophthalmic solution or an ointment, the oral route being preferred.
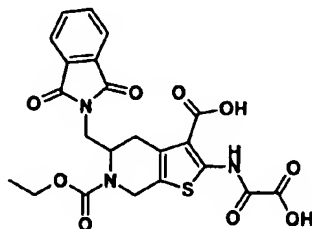
EXAMPLES

The process for preparing compounds of Formula 1 and preparations containing them is further illustrated in the following examples, which, however, are not to be construed as limiting.

5   Hereinafter, TLC is thin layer chromatography, CDCl₃ is deuterio chloroform, CD₃OD is tetradeuterio methanol and DMSO-d₆ is hexadeuterio dimethylsulfoxide. The structures of the compounds are confirmed by either elemental analysis or NMR, where peaks assigned to characteristic protons in the title compounds are presented where appropriate. ^{1}H NMR shifts (δ_H) are given in parts per million (ppm) down field from tetramethylsilane as internal refer-

10   ence standard. M.p.: is melting point and is given in °C and is not corrected. Column chromatography was carried out using the technique described by W.C. Still *et al.*, *J. Org. Chem. 43:* 2923 (1978) on Merck silica gel 60 (Art. 9385). HPLC analyses are performed using 5µm C18 4 x 250 mm column eluted with various mixtures of water and acetonitrile, flow = 1 ml/min, as described in the experimental section.

15   Compounds used as starting material are either known compounds or compounds, which can readily be prepared by methods known per se.

EXAMPLE 1

20   5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid 6-ethyl ester

To a solution of 4-(2-spiro[1,3]dioxolane)-piperidine (51.5 g, 0.36 moles) in a mixture of dichloromethane (500 ml) and saturated sodium bicarbonate (500 ml) was added di-*tert*-butyldicarbonate (69.8 g, 0.32 moles) and the reaction was vigorously stirred for 3 hours and

25   the layers separated. The organic layer was washed with 1N hydrochloric acid (2 x 150 ml), brine (100 ml), dried (MgSO₄), filtered and the solvent evaporated in vacuo affording 75.5 g (97 %) of 4-(2-spiro[1,3]dioxolane)-piperidine-1-carboxylic acid *tert*-butyl ester as a crystallizing oil.

^{1}H-NMR (400 MHz, CDCl₃): δ 3.96 (s, 4H), 3.49 (bm, 4H), 1.65 (bm, 4H), 1.45 (s, 9H).

30   To the above 4-(2-spiro[1,3]dioxolane)-piperidine-1-carboxylic acid *tert*-butyl ester (4.0 g, 16.4 mmol) dissolved in dry diethyl ether (32 ml) was added 2,2' bipyridyl (1 mg) and

45

the solution was cooled to −75 °C. Tetramethyl-ethylenediamine (3.2 ml, 21.4 mmol) was added followed by dropwise addition of sec-butyl lithium (16.4 ml, 21.4 mmol, 1.3M in cyclo-hexane). The mixture was stirred at -75 °C for 10 min, then slowly warmed to -20 °C and stirred at that temperature for 0.5 hour, then cooled to -30 °C. At this temperature, formaldehyde

5   was generated by heating paraformaldehyde at 150 °C and passed through the mixture with dry nitrogen until the color faded to off-white, at which time water (40 ml) was added. The layers were separated, and the aqueous layer was extracted with diethyl ether (2 x 50 ml). The combined organic extracts were washed with 1N hydrochloric acid (2 x 75 ml), saturated sodium bicarbonate solution (50 ml), dried (MgSO$_4$), filtered and the solvent evaporated in

10   vacuo. The residue (2.9 g) was purified by silica gel chromatography (hexane/ethyl acetate, 10 % ethyl acetate to 30 % ethyl acetate, gradient). Pure fractions were collected and the solvent evaporated in vacuo affording 1.3 g (29 %) of 2-hydroxymethyl-4-(2-spiro[1,3]dioxolane)-piperidine-1-carboxylic acid tert-butyl ester as a thick oil.

^{1}H-NMR (400 MHz, CDCl$_3$): δ 4.42 (bm, 1H), 4.08-3.96 (m, 5H), 3.96-3.88 (m, 1H), 3.78-3.70

15   (m, 1H), 3.30-3.16 (bm, 1H), 2.30-1.98 (bs, 1H), 1.96-1.78 (m, 2H), 1.74-1.64 (m, 2H), 1.49 (s, 9H).

       To 2-hydroxymethyl-4-(2-spiro[1,3]dioxolane)-piperidine-1-carboxylic acid tert-butyl ester (0.4 g, 1.5 mmol) dissolved in dry tetrahydrofuran (20 ml) was added phthalimide (0.28 g, 1.9 mmol), triphenylphosphine (0.5 g, 1.9 mmol) and the mixture was cooled to 0 °C in an

20   ice bath. Diethyl azodicarboxylate (0.29 ml, 1.82 mmol) was added dropwise and the mixture was stirred at 0 °C for 0.5 hour, then at ambient temperature for 18 hours. The solvent was removed in vacuo and the residue was purified by silica gel chromatography (hexane/ethyl acetate, 18 % ethyl acetate to 25 % ethyl acetate, gradient). Pure fractions were collected and the solvent evaporated in vacuo affording 0.29 g (48 %) of 2-(1,3-dioxo-1,3-dihydro-

25   isoindol-2-ylmethyl)-4-(2-spiro[1,3]dioxolane)-piperidine-1-carboxylic acid tert-butyl ester.

^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.94-7.80 (bs, 2H), 7.80-7.64 (bd, 2H), 4.96-4.70 (2bs, 1H), 4.66-4.52 (m, 1H), 4.30-4.14 (bm, 1H), 4.12-4.04 (m, 2H), 4.04-3.94 (m, 2H), 3.56-3.32 (m, 2H), 2.04-1.92 (m, 1H), 1.90-1.60 (m, 4H), 1.22-1.00 (bs, 9H).

MS: m/z: 403 [M+H]$^+$, 303 [M–Boc]

30   To the above 2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-(2-spiro[1,3]dioxolane)-piperidine-1-carboxylic acid tert-butyl ester (1.1 g, 2.7 mmol) dissolved in dichloromethane (6 ml) was added 1.0 N hydrogen chloride in diethyl ether (50 ml) and the solution kept at ambient temperature for 62 hours. The precipitate was filtered off and washed with diethyl ether and dried with nitrogen which afforded 0.83 g (90 %) of 2-(1,3-dioxo-1,3-dihydro-isoindol-2-

35   ylmethyl)-4-(2-spiro[1,3]dioxolane)-piperidine hydrochloride as a solid.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ 9.2-8.8 (2bs, 2H), 7.8-8.1 (m, 2H), 4,1-3.6 (m, 5H), 2.9 (bs, 1H), 2.2-1.6 (m, 5H).

MS: m/z: 303.5 [M+H]$^+$

To a suspension of the above 2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-(2-

5   spiro[1,3]dioxolane)-piperidine hydrochloride (0.7 g, 2.1 mmol) and ethyl chloroformate (0.24 ml, 2.5 mmol) in dry tetrahydrofuran (14 ml) cooled in an ice bath under nitrogen was added diisopropyl-ethylamine (0.95 ml, 5.4 mmol) and the reaction mixture was stirred at ambient temperature for 3 hours. The volatiles were removed in vacuo and the residue was partitio-ned between dichloromethane (25 ml) and 1N hydrochloric acid (25 ml). The layers were se-

10   parated, and the aqueous layer extracted with dichloromethane (20 ml). The combined orga-nic extracts were washed with a saturated sodium bicarbonate solution (50 ml), dried (MgSO$_4$), filtered and the solvent evaporated in vacuo. The residue was triturated with n-butylchloride, filtered and dried with nitrogen which afforded 0.47 g (61 %) of 2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-(2-spiro[1,3]dioxolane)-piperidine-1-carboxylic acid ethyl

15   ester as an oil.

^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.9 (s, 2H), 7.7(s, 2H), 4.9-4.7 (bs, 1H), 4.7-4.5 (m, 1H), 4.3-3.9 (m, 5H), 3.9-3.6 (bs, 1H), 3.6-3.3 (m, 2H), 2.0-1.9 (m, 1H), 1.9-1.5 (m, 4H), 1.1-0.7 (bs, 3H).

MS: m/z: 373 [M-H]$^-$.

20

A solution of the above 2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-(2-spiro[1,3]dioxolane)-piperidine-1-carboxylic acid ethyl ester (0.44 g, 1.2 mmol) in a mixture of 1N hydrochloric acid (18 ml) and tetrahydrofuran (18 ml) was heated a 75 °C under nitrogen with stirring for 18 hours. The tetrahydrofuran was removed in vacuo and the residue was

25   extracted with dichloromethane (2 x 75 ml). The combined organic extracts were washed with a saturated sodium bicarbonate solution (50 ml), dried (MgSO$_4$), filtered and the solvent removed in vacuo affording 0.42 g (> 100 %) of 2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-oxo-piperidine-1-carboxylic acid ethyl ester as a solid.

^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.9 (s, 2H), 7.8 (s, 2H), 5.3-5.0 (bm, 1H), 4.6-4.2 (bm, 1H), 4.0

30   (m, 2H), 3.8-3.6 (bm, 3H), 2.8 (m, 1H), 2.7-2.4 (bm, 3H), 1.0 (bs, 3H).

MS: m/z: 330.6 [M+H]$^+$.

A mixture of the above 2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-oxo-piperidine-1-carboxylic acid ethyl ester (0.39 g, 1.2 mmol), tert-butyl cyanoacetate (0.22 g, 1.55 mmol), sulfur (42 mg, 1.3 mmol) in ethanol (1.5 ml) was degassed. To this mixture, under nitrogen,

35   morpholine (205 μl) was added and the mixture was heated a 50 °C for 13 hours. The solvent was removed in vacuo. The residue (0.74 g) was purified by silica gel chromatography using

a mixture of hexane/ethyl acetate (7:3) as eluent. Pure fractions were collected and the solvent evaporated in vacuo. The residue (0.29 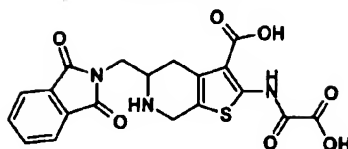g) was titurated with acetonitrile, filtered, and dried with nitrogen affording 84 mg (15 %) of 2-amino-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-

5   ethyl ester.

^{1}H-MNR (400 MHz, CDCl$_3$): δ 7.9-7.7 (2m, 4H), 6.0 (bs, 2H), 5.1-4.8 (bm, 1H), 4.8-4.5 (m, 1H), 4.5-4.2 (m, 1H), 4.1-3.4 (3m, 4H), 3.0 (m, 2H), 1.8-1.4 (m, 10H), 1.1-0.9 (m, 3H). MS: m/z: 486 [M+H]$^+$.

To the above 2-amino-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-

10   tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (48 mg, 0.1 mmol) dissolved in dry tetrahydrofuran (1 ml) was added imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.4 ml) and the solution stirred for 18 hours at ambient temperature. The solvent was removed in vacuo and the residue was dissolved in dichloromethane (25 ml) and a saturated sodium bicarbonate solution (25 ml) was added. The layers were separated and

15   the aqueous layer was extracted with dichloromethane (25 ml). The combined organic extracts were dried (Na$_2$SO$_4$), filtered and the solvent evaporated in vacuo. The residue (63 mg) was dissolved in ethyl acetate and passed through 1 g of silica gel and the solvent evaporated in vacuo affording 55 mg (90 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid 3-*tert*-butyl

20   ester 6-ethyl ester as a solid.

The above 2-(*tert*-butoxyoxalyl-amino)-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (55 mg, 0.09 mmol) was dissolved in 50 % trifluoroacetic acid in dichloromethane (2 ml) and stirred at ambient temperature for 18 hours. The volatiles were removed in vacuo and the

25   residue was purified by preparative HPLC (column: Kromasil C18, 250 x 4.6 mm., flow: 2 ml/min., gradient: acetonitrile/water, 20 % acetonitrile to 60 % acetonitrile over 20 min.) affording after evaporation of the solvent in vacuo 13.8 mg (31 %) of the title compound as a solid trifluoroacetate.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ 14-13 (bs, 1H), 12.4 (s, 1H), 7.9 (s, 4H), 4.9 (m, 2H), 4.4

30   (m, 1H), 4.0-2.8 (m, 13H), 0.8 (m, 3H). MS: m/z: 502 [M+H]$^+$.

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EXAMPLE 2

5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

2-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-(2-spiro[1,3]dioxolane)-piperidine-1-carboxylic acid *tert*-butyl ester (353 mg, 0.88 mmol) was cooled in an ice bath and then dissolved in a solution of 20 % trifluoroacetic acid/dichloromethane (7 ml). The reaction was stirred for 5 minutes in the ice bath then another 3 hours at ambient temperature, after which it was concentrated in vacuo affording a solid residue. To the solid was added 2N hydrochloric acid (9 ml) and the mixture was heated at 50 °C (oil bath) with stirring for 24 hours. The cooled reaction mixture was quenched with saturated sodium bicarbonate solution until the pH was basic. The aqueous layer was extracted with chloroform (3 x 20 ml) and the combined organic extracts dried (K_2CO_3), filtered, and the solvent evaporated in vacuo to give 205 mg (91 %) of 2-(4-oxo-piperidin-2-ylmethyl)-isoindole-1,3-dione as a solid.

^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.90-7.83 (m, 2H), 7.78-7.71 (m, 2H), 3.81-3.73 (m, 2H), 3.43-3.35 (m, 1H), 3.30-3.22 (m, 1H), 2.83 (dt, 1H, J = 13 Hz and J = 3 Hz), 2.46 (d, 1H, J = 15 Hz), 2.42-2.32 (m, 2H), 2.21 (dd, 1H, J = 14 Hz and J = 13 Hz).

APCI-MS: m/z: 259 [M+H]$^+$

The above 2-(4-oxo-piperidin-2-ylmethyl)-isoindole-1,3-dione (0.20 g, 0.76 mmol) was dissolved in dichloromethane (5 ml). Saturated sodium bicarbonate solution (5 ml) was added followed by di-*tert*-butyl dicarbonate (0.20 g, 0.91 mmol). The reaction was stirred vigorously for 16 hours after which the organic phase was separated. The aqueous layer was extracted with dichloromethane (2 x 10 ml) and the combined organic extracts were dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography using a gradient of ethyl acetate/dichloromethane (0 to 10 % gradient) as eluent. Pure fractions were collected and the solvent evaporated in vacuo affording 0.23 g (85 %) of 2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester.

^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.86 (bs, 2H), 7.72 (bs, 2H), 5.15-4.98 (m, 1H), 4.23-4.14 (m, 1H), 3.90 (t, 1H, *J* = 12 Hz), 3.61-3.52 (m, 2H), 2.78-2.70 (m, 1H), 2.57-2.39 (m, 3H), 1.15 (s, 9H).

APCI-MS: m/z: 359 [M+H]$^+$

The above 2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (0.43 g, 1.2 mmol) was dissolved in absolute ethanol (9 ml). To the solution was added sulfur (42 mg, 1.32 mmol) and *tert*-butyl cyanoacetate (0.22 g, 1.56 mmol). The mixture was placed under nitrogen and stirred in a 50 °C oil bath. Morpholin (0.21 ml, 2.4

5   mmol) was added and the reaction was stirred for 16 hours. The precipitate formed was filtered off and washed with acetonitrile (2 x 3 ml) and dried which afforded 0.18 g of 2-amino-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester **(A)** (30 %). The filtrate was concentrated in vacuo and the residue purified by silica gel chromatography using a gradient of ethyl acetate/hexane (1:4 to

10   1:3 gradient) as eluent. Pure fractions were collected and the solvent evaporated in vacuo affording 0.3 g of a mixture of 2-amino-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester and 2-amino-7-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester. HPLC purification of a small portion of the mixture gave

15   28 mg of pure 2-amino-7-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester **(B)**.

(A):

^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.87-7.82 (m, 2H) 7.73-7.66 (m, 2H), 6.00 (bs, 2H), 5.02-4.87

20   (m, 1H), 4.72-4.21 (m, 2H), 4.03-3.93 (m, 1H), 3.51 (t, 1H, J = 14 Hz), 2.97-2.91 (m, 2H), 1.56 (s, 9H), 1.12-1.09 (s, 9H).
LC-MS: R$_t$=3.96 min, m/z: 514.4 [M+H]$^+$

(B):

25   ^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.88-7.82 (m, 2H), 7.74-7.66 (m, 2H), 5.39-5.19 (m, 1H), 4.30-4.02 (m, 2H), 3.78-3.70 (m, 1H), 3.33-3.18 (m, 1H), 2.86 (dd, 1H, J = 18 Hz and J = 4 Hz), 2.75-2.61 (m, 1H), 1.54 (s, 9H), 1.13-1.05 (s, 9H).
LC-MS: R$_t$=4.01 min, m/z: 514.4 [M+H]$^+$

30   To a solution of the above 2-amino-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester (50 mg, 0.097 mmol) in dichloromethane (3 ml) was added imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (60 mg, 0.29 mmol). The reaction was placed under nitrogen and stirred for 3 hours at ambient temperature. The solution was concentrated in vacuo and the residue purified by silica gel chro-

35   matography using a 5 % mixture of ethyl acetate/ dichloromethane as eluent. Pure fractions were collected and the solvent evaporated in vacuo affording 54 mg (87 %) of 2-(*tert*-

butoxyoxalyl-amino)-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-
thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester.

^{1}H-NMR (400 MHz, CDCl$_3$): δ 12.52 (s, 1H), 7.85 (bs, 2H), 7.74-7.67 (m, 2H), 5.08-4.92 (m,

1H), 4.93-4.40 (m, 2H), 3.97-3.87 (m, 1H), 3.53 (t, 1H, J = 14 Hz), 3.11-2.99 (m, 2H), 1.62 (s,

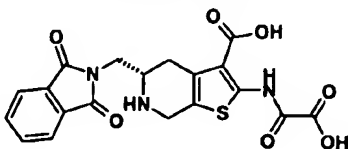5   18H), 1.14-1.12 (2s, 9H).

APCI-MS: m/z: 641 [M-H]⁻

The above 2-(*tert*-butoxyoxalyl-amino)-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-

4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester (54 mg, 0.084

mmol) was dissolved in a solution of 50 % trifluoroacetic acid/dichloromethane (2 ml). The

10   reaction was stirred at ambient temperature for 7 hours, concentrated in vacuo and the resi-

due evaporated in vacuo from dichloromethane (3 x 10 ml). The resulting precipitate was

washed with dichloromethane, filtered off and dried in vacuo, which afforded 41 mg (90 %) of

the title compound as a solid trifluoroacetate.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ 12.31 (s, 1H), 9.36 (bs, 2H), 7.93-7.90 (m, 2H), 7.88-7.85

15   (m, 2H), 4.43 (d, 1H, J = 16 Hz), 4.26 (d, 1H, J = 16 Hz), 4.03-3.91 (m, 2H), 3.83-3.76 (m,

1H), 3.31 (dd, 1H, J = 18 Hz and J = 4 Hz), 2.82 (dd, 1H, J = 18 Hz and J = 10 Hz).

APCI-MS: m/z: 430 [M+H]⁺

HPLC (254.4nm): R$_t$=6.72 min, 98 %

20

EXAMPLE 3

5-(*S*)-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-
thieno[2,3-c]pyridine-3-carboxylic acid

25   To a solution of L-aspartic acid (120 g, 0.90 mol) in methanol (600 ml) cooled to -20 °C was

added thionylchoride (93 ml, 1.29 mol) dropwise over 0.5 hour. The cooling bath was re-

moved and the mixture was stirred for 1 hour, before diethyl ether (1.8 L, containing 50 ml 1

N hydrochloric acid in diethyl ether) was added upon cooling. The resulting precipitate was

filtered off and washed with diethyl ether. The product was recrystallized twice:

30   First recrystallization: The product was dissolved in warm methanol (600 ml) and reprecipi-

tated with 1.8 ml diethyl ether (containing 50 ml 1 N hydrochloric acid in diethyl ether).

Second recrystallization: The product was dissolved in warm methanol (250 ml) and repre-
cipitated with 1.0 m diethyl ether (containing 50 ml 1 N hydrochloric acid in diethyl ether).

This afforded 75 g (45 %) of L-aspartic acid β-methyl ester hydrochloride as a solid.

To a solution of the above β-methyl ester (50 g, 0.27 mol) in water (120 ml) cooled to

5   0 °C was added triethylamine (95 ml, 0.68 mol) and methyl acrylate (74 ml, 0.82 mol). The
reaction mixture was stirred for 3 hours before the cooling bath was removed. After stirring
for an additional 1 hour the mixture was washed with petrol ether (2 x 400 ml), before tert-
butanol (40 ml) and di-tert-butyl dicarbonate (74 g, 0.34 mol) was added and the reaction
mixture was stirred for 16 hours. The mixture was washed with petrol ether (2 x 400 ml),

10   cooled to 0 °C and the pH adjusted to 3 with concentrated hydrochloric acid. After extraction
with ethyl acetate (3 x 200 ml) the organic phase was washed with brine (200 ml), dried
(MgSO₄), filtered and the volatiles evaporated in vacuo. The residue was subjected to col-
umn chromatography on silicagel using a mixture of ethyl acetate/hexane/methanol/acetic
acid (25:25:2.5:1) as eluent. Pure fractions were collected and the solvent evaporated in

15   vacuo which afforded 60 g (66 %) of 2-(tert-butoxycarbonyl-(2-methoxycarbonyl-ethyl)-
amino)-succinic acid 4-methyl ester as a solid.

To a solution of the above di-ethyl ester (96.9 g, 0.29 mol) in dry degassed tetrahy-
drofuran (1.0 l) was added sodium methoxide (161 ml, 30% solution in methanol) and the
reaction mixture was refluxed under nitrogen for 16 hours with mechanical stirring. The reac-

20   tion mixture was cooled to room temperature; the volatiles remove in vacuo until a wet cage
was observed. Water (500 ml) was added and the reaction mixture was refluxed for 16
hours. The remaining organic solvents were evaporated in vacuo before the pH was adjusted
to 2.5 with concentrated hydrochloric acid. The aqueous phase was extracted with ethyl ace-
tate (3 x 300 ml) and the combined organic phases were washed with brine (100 ml), dried

25   (MgSO₄) and filtered. tert-Butyl amine (25.36 g, 0.350 mol) was added dropwise under stir-
ring whereupon a off white precipitate was formed. The precipitate was filtered off and
washed with ethyl acetate, dried in vacuo affording 74.4 g (81 %) of 4-oxo-piperidine-1,2-
dicarboxylic acid 1-tert-butyl ester, tert-butyl amine salt as a solid.

Analytically pure compound can be obtained from recrystallisation of the crude prod-

30   uct from ethanol-diisopropyl ether by heating the compound in ethanol (ca 100 ml per 10 g
compound) and while still hot diisopropyl ether is added (ca 250 ml per 10 g compound).
Yield in recrystallisation is approximately 50 %.

A solution of the above 4-oxo-piperidine-1,2-dicarboxylic acid 1-tert-butyl ester, tert-
butyl amine salt (3.0 g, 9.48 mmol), tert-butyl cyanoacetate (2.01 g, 14.22 mmol), sulfur (0.46

35   g, 14.22 mmol) and diisopropyl-ethylamine (1.64 ml, 9.48 mmol) was heated to 50 °C under
nitrogen for 12 hours. The solution was allowed to cool to room temperature before a small

precipitate was filtered off. The filtrate was evaporated in vacuo and the residue was divided
between ethyl acetate (50 ml) and saturated ammonium chloride (100 ml). The aqueous
phase was extracted with ethyl acetate (3 x 50 m) and the combined organic phases were
washed with brine (50 ml), dried (MgSO$_4$), filtered and the solvent evaporated in vacuo. The
5   residue was subjected to column chromatography using a mixture of petrol ether/ethyl ace-
tate/methanol (8:4:1) as eluent. Pure fractions were collected and the solvent evaporated in
vacuo affording 2.22 g (58 %) of 2-amino-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,5,6-
tricarboxylic acid 3,6-di-tert-butyl ester as a solid.

10   To a solution of the above 3,5,6-tricarboxylic acid 3,6-di-tert-butyl ester (0.63 g, 1.58
mmol) in dimethoxyethane (10 ml) cooled to -20 °C was added N-methylmorpholine (174 ml,
1.58 mmol) followed by isobutylchoroformate (205 ml, 1.58 mmol) and the reaction mixture
was stirred for two min. before a precipitate was filtered off. The precipitate was rapidly
washed with dimethoxyethane (2 x 2.5 ml), recooled to -20 °C and a solution of sodium
15   borohydride (90 mg, 2.37 mmol) in water (1 ml) was added in one lot to the filtrate. (Caution -
gas evolution).

The reaction mixture was stirred until gas evolution ceases (app. 3 min.) and the mix-
ture was poured into water (25 ml) and extracted with ethyl acetate (10 ml), washed with
brine (5 ml), dried (MgSO$_4$), filtered and the solvent evaporated in vacuo affording 0.40 g (66
20   %) of 2-amino-5-(S)-hydroxymethyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic
acid di-tert-butyl ester as a solid.

To a mixture of the above 2-amino-5-(S)-hydroxymethyl-4,5,6,7-tetrahydro-thieno[2,3-
c]pyridine-3,6-dicarboxylic acid di-tert-butyl ester (2.00 g, 5.20 mmol), phthalimide (0.92 g,
6.24 mmol) and triphenylphosphine (1.64 g, 6.24 mmol) in dry tetrahydrofuran (30 ml) cooled
25   to 0 °C under a nitrogen atmosphere was added diethyl azodicarboxylate (DEAD) (0.98 ml,
6.24 mmol). The reaction mixture was allowed to stir overnight, slowly warming to room tem-
perature. Next day the reaction mixture was again cooled to 0 °C and phthalimide (0.46 g,
3.12 mmol), triphenylphosphine (0.82 g, 3.12 mmol) and diethyl azodicarboxylate (DEAD)
(0.49 ml, 3.12 mmol) was added in sequence and the reaction mixture was allowed to stir
30   overnight, slowly warming to room temperature. The volatiles were evaporated in vacuo and
the resultant solid dissolved in dichloromethane (20 ml). The residue was subjected to flash
column chromatography using a mixture of ethyl acetate/hexane (1:2) as eluent. Fractions
were collected affording after evaporation in vacuo 1.0 g of the desired compound contami-
nated with phthalimide. Recrystallization from ethanol gave 0.23 g (9 %) of pure 2-amino-5-
35   (S)-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-
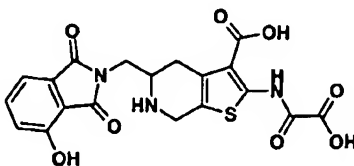dicarboxylic acid di-tert-butyl ester as a solid.

To the above di-*tert*-butyl ester (0.20 g, 0.39 mmol) dissolved in dichloromethane (4 ml) was added a mixture of imidazol-1-yl-oxo-acetic acid *tert* butyl ester (0.23 g, 1.17 mmol) in dichloromethane (1 ml) under nitrogen. The reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was added dichloromethane (5 ml) and washed

5   with 1 % hydrochloric acid (10 ml), dried (Na_2SO_4), filtered and the organic phase evaporated in vacuo affording 0.25 g (100 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(*S*)-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester.

The above tri-*tert*-butyl ester (0.25 g, 0.39 mmol) was dissolved in 20 % trifluoroacetic

10 acid in dichloromethane (5 ml). The reaction was stirred at room temperature for 24 hours before diethyl ether (5 ml) was added. The precipitate was filtered off, washed with diethyl ether, dried in vacuo to give 150 mg of a solid. NMR revealed the presence of a trace amount of material arising from incomplete deprotection. 100 mg of the crude product was redissolved in 20 % trifluoroacetic acid in dichloromethane (5 ml), and stirred at room tem-

15 perature for 24 hours before diethyl ether (5 ml) was added. The product was filtered off and washed with diethyl ether and dried in vacuo to give 50 mg (40 %) of the title compound as a solid trifluoroacetate.

M.p.: dec.> 240 °C

Calculated for $C_{19}H_{15}N_3O_7S$, $1/3xC_2HF_3O_2$, $0.5xH_2O$;

20 C, 49.58 %; H, 3.46 %; N, 8.82 %. Found:

C, 49.84 %; H, 3.83 %; N, 8.99 %.

EXAMPLE 4

25 7-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

To a solution of pure 2-amino-7-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester (28 mg, 0.057 mmol)

30 in dichloromethane (2 ml) was added midazol-1-yl-oxo-acetic acid *tert*-butyl ester (35 mg, 0.17 mmol). The reaction was placed under nitrogen and stirred for 12 hours at ambient tem-

perature. The volatiles were evaporated in vacuo and the residue was purified by silica gel chromatography using a mixture of ethyl acetate/ hexane (1:3) as eluent. Pure fractions were collected and the solvent evaporated in vacuo affording 25 mg (67 %) of 2-(tert-butoxyoxalyl-amino)-7-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-
5   3,6-dicarboxylic acid di-tert-butyl ester as an oil.

^{1}H-NMR (400 MHz, CDCl$_3$): δ 12.59-12.53 (bs, 1H), 7.89-7.84 (m, 2H), 7.75-7.67 (m, 2H), 5.61-5.41 (m, 1H), 4.36-4.15 (m, 1H), 4.12-4.06 (m, 1H), 3.90-3.82 (m, 1H), 3.34-3.21 (m, 1H), 2.99-2.93 (m, 1H), 2.84-2.68 (m, 1H), 1.62-1.59 (s, 18H), 1.12-1.06 (s, 9H).

The above 2-(tert-butoxyoxalyl-amino)-7-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-
10   4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-tert-butyl ester (25 mg, 0.039 mmol) was dissolved in a solution of 50 % trifluoroacetic acid/dichloromethane (1.5 ml). The reaction was stirred at ambient temperature for 7 hours, concentrated in vacuo and the resi-due evaporated in vacuo from dichloromethane (3 x 10 ml). The resulting precipitate was washed with dichloromethane, filtered off and dried in vacuo to give 41 mg (85 %) of the title
15   compound as a solid trifluoroacetate.

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ 12.32 (s, 1H), 9.48 (bs, 2H), 7.95-7.91 (m, 2H), 7.89-7.84 (m, 2H), 4.89 (s, 1H), 4.15-4.07 (m, 2H), 3.43-3.28 (2m, 2H, partially obscured by water), 3.04 (bs, 2H).

LC-MS: R$_t$=1.51 min, m/z: 428.4 [M-H]$^-$

20

EXAMPLE 5

5-(4-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-
25   thieno[2,3-c]pyridine-3-carboxylic acid

7-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-1,4-dioxa-8-aza-spiro[4.5]decane-8-carboxylic acid tert-butyl ester (1.55 g, 3.85 mmol) was cooled in an ice bath and then dissolved in a solution of 20 % trifluoroacetic acid/dichloromethane (15 ml). The reaction was stirred and
30   allowed to slowly warm to ambient temperature during 3 hours. The solution was concentra-ted in vacuo to give crude 2-(1,4-dioxa-8-aza-spiro[4.5]dec-7-ylmethyl)isoindole-1,3-dione which was used directly in the following step (assumed 100 % yield).

^{1}H-NMR (400 MHz, CDCl$_3$): δ 9.26 (bs, 1H), 8.19 (bs, 1H), 7.78-7.75 (m, 2H), 7.74-
7.71 (m, 2H), 4.11-3.98 (m, 5H), 3.90-3.79 (m, 3H), 3.26-3.17 (m, 1H), 2.10-2.00 (m, 3H),
1.92-1.88 (m, 1H).

To a suspension of the above 2-(1,4-dioxa-8-aza-spiro[4.5]dec-7-ylmethyl)isoindole-

5   1,3-dione (3.85 mmol) in absolute ethanol (25 ml) was added hydrazine (0.36 ml, 11.55
mmol). The reaction was stirred at 80 °C (oil bath) for 6 hours, then cooled to ambient tempe-
rature and stirred for an additional 12 hours. The thick precipitate was filtered off and washed
with ethanol. The filtrate was concentrated in vacuo and reconstituted in dichloromethane (20
ml), forming a small amount of a second precipitate, which was filtered off. The filtrate was

10   evaporated in vacuo and the resulting oil was dissolved in water (10 ml) and basified with 1N
sodium hydroxide until pH = 10. The aqueous layer was extracted with 20 % isopropyl alco-
hol/chloroform (12 x 40 ml). The combined organic extracts were dried (K$_2$CO$_3$), filtered and
the solvent evaporated in vacuo affording 0.42 g (63 %) of (1,4-dioxa-8-aza-spiro[4.5]dec-7-
yl)methylamine as an oil.

15   ^{1}H-NMR (300 MHz, CDCl$_3$): δ 3.94 (bs, 4H), 3.11-3.05 (m, 1H), 2.81 (dt, 1H, J = 12
Hz and J = 3 Hz), 2.76-2.65 (m, 2H), 2.58-2.50 (m, 1H), 1.70-1.57 (m, 3H), 1.31 (t, 1H, J = 12
Hz).

APCI-MS: m/z: 173.2 [M+H]$^+$

To a solution of 4-hydroxy-isobenzofuran-1,3-dione (0.51 g, 3.09 mmol) in anhydrous

20   N,N-dimethylformamide (7 ml) under nitrogen was added sodium hydride (130 mg, 3.25
mmol). Immediate evolution of gas and bright yellow color was observed. The mixture was
stirred for 5 minutes after which benzyl bromide (1.8 ml, 15.45 mmol) was added. The reac-
tion was stirred for 72 hours. Saturated sodium bicarbonate (2 ml) was added and the mix-
ture stirred for 2 minutes, diluted in ethyl acetate (35 ml) and washed with saturated sodium

25   bicarbonate (5 ml), 1N hydrochloric acid (5 ml), and brine (2 x 5 ml). The organic layer was
dried (MgSO$_4$), filtered and the solvent evaporated in vacuo. To the crude material was ad-
ded hexane and the formed precipitate was filtered off, washed further with hexane and dried
in vacuo to give 0.54 g (69 %) of 4-(benzyloxy)-isobenzofuran-1,3-dione as a solid.

^{1}H-NMR (300 MHz, CDCl$_3$): δ 7.74 (t, 1H, J = 8 Hz), 7.54 (d, 1H, J = 8 Hz), 7.47-7.29 (m,

30   6H), 5.36 (s, 2H).

A solution of (1,4-dioxa-8-aza-spiro[4.5]dec-7-yl)methylamine (0.19 g, 1.1 mmol) and
4-(benzyloxy)-isobenzofuran-1,3-dione (0.27 g, 1.05 mmol) was prepared in a mixture of
distilled dichloromethane (3 ml) and anhydrous N,N-dimethylformamide (2.5 ml) under nitro-
gen. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.23 g, 1.21 mmol) was

35   added followed by triethylamine (0.46 ml, 3.3 mmol) and the reaction stirred at ambient tem-
perature for 18 hours. The solution was concentrated in vacuo and the residue diluted with

ethyl acetate (25 ml) and washed with water (5 ml), saturated sodium bicarbonate (5 ml), and brine (5 ml). The organic layer was evaporated in vacuo and the residue purified by silica gel chromatography using a mixture of 5 % methanol/dichloromethane/1 % triethylamine as eluent. Pure fractions were collected and the solvent evaporated in vacuo affording 0.22 g

5   (50 %) of 4-benzyloxy-2-(1,4-dioxa-8-aza-spiro[4.5]dec-7-ylmethyl)-isoindole-1,3-dione as a semi-solid.

^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.57 (t, 1H, J = 8 Hz), 7.48 (d, 2H, J = 7 Hz), 7.42-7.29 (m, 4H), 7.18 (d, 1H, J = 8 Hz), 5.31 (s, 2H), 3.94-3.90 (m, 4H), 3.65 (d, 2H, J = 6 Hz), 3.16-3.09 (m, 1H), 3.07-3.02 (m, 1H), 2.76 (dt, 1H, J = 13 Hz and J = 3 Hz), 1.78 (d, 1H, J = 12

10   Hz), 1.64-1.54 (m, 3H), 1.37 (t, 1H, J = 12 Hz), 1.08 (t, 1H, J = 7 Hz).

LC-MS: R$_t$=2.59 min, m/z: 409 [M+H]$^+$

To a solution of the above 4-benzyloxy-2-(1,4-dioxa-8-aza-spiro[4.5]dec-7-ylmethyl)-isoindole-1,3-dione (0.22 g, 0.54 mmol) in 1,4-dioxane (4 ml) was added 4N hydrochloric acid (4 ml) and the reaction stirred in a 65 °C (oil bath) for 6 hours. The mixture was basified

15   with saturated sodium bicarbonate until pH = 8 and extracted with dichloromethane (3 x 20 ml). The combined organic extracts were dried (MgSO$_4$), filtered, and the solvent evaporated in vacuo affording crude 4-benzyloxy-2-(4-oxo-piperidin-2-ylmethyl)-isoindole-1,3-dione as an oil. Which was used without further purification or characterization.

The above crude 4-benzyloxy-2-(4-oxo-piperidin-2-ylmethyl)-isoindole-1,3-dione (0.17

20   g, 0.47 mmol) was dissolved in dichloromethane (4 ml). Saturated sodium bicarbonate (4 ml) was added followed by di-tert-butyl dicarbonate (0.11 g, 0.52 mmol). The reaction was stirred vigorously for 16 hours, and then the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 10 ml) and the combined organic phases were dried (MgSO$_4$), filtered and the solvent evaporated in vacuo. The residue was purified by silica gel chroma-

25   tography using a mixture of ethyl acetate/hexane (1:2) as eluent. Pure fractions were collected and the solvent was evaporated in vacuo affording 0.14 g (64 %) of 2-(4-benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-oxo-piperidine-1-carboxylic acid tert-butyl ester.

^{1}H-NMR (400 MHz, CDCl$_3$): δ 7.57 (bs, 1H), 7.47-7.31 (m, 6H), 7.18 (bs, 1H), 5.34 (s, 2H), 5.03 (bs, 1H), 4.45-4.14 (m, 1H), 3.89 (t, 1H, J = 12 Hz), 3.55 (bs, 2H), 2.76-2.71 (m, 1H),

30   2.57-2.38 (m, 3H), 1.17 (s, 9H).

A solution of 2-(4-benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-oxo-piperidine-1-carboxylic acid tert-butyl ester (0.14 g, 0.30 mmol), sulfur (10.6 mg, 0.33 mmol), and tert-butyl cyanoacetate (55 mg, 0.39 mmol) in absolute ethanol (4 ml) was stirred at 50 °C (oil bath). Morpholine (53 µl, 0.6 mmol) was added and the reaction placed under nitrogen

35   and stirred for 16 hours. The solution was cooled to ambient temperature, concentrated in vacuo and the residue purified by silica gel chromatography using a gradient of ethyl aceta-

te/dichloromethane (0 to 5 % gradient) as eluent. Pure fractions were collected and the solvent evaporated in vacuo affording a mixture of regioisomers 0.15 g (80 %) of 2-amino-5-(4-benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester and 2-amino-7-(4-benzyloxy-1,3-dioxo-1,3-dihydro-

5   isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester which were not separable by chromatography.

To a solution of the above mixture of 2-amino-5-(4-benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester and 2-amino-7-(4-benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-

10   tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester (0.15 g, 0.24 mmol) in distilled dichloromethane (4 ml) under nitrogen was added imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.14 g, 0.72 mmol) and the reaction mixture was stirred at ambient temperature for 1.5 hour. The volatiles were evaporated in vacuo and the crude residue was purified by silica gel chromatography using dichloromethane as eluent. Pure fractions were collected
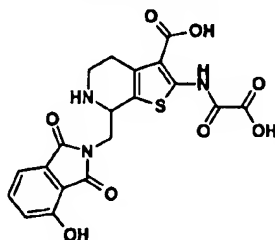
15   and the solvent evaporated in vacuo affording 50 mg of 2-(*tert*-butoxyoxalyl-amino)-5-(4-benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester (**A**) and 50 mg of 2-(*tert*-butoxyoxalyl-amino)-7-(4-benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester (**B**). Another 50 mg remained as a mixture of the two

20   isomers (**A**) and (**B**).

(A):

^{1}H-NMR (300 MHz, CDCl$_3$): δ 12.52 (s, 1H), 7.60-7.31 (m, 7H), 7.20-7.10 (m, 1H), 5.33 (s, 2H), 5.05-4.38 (m, 3H), 3.96-3.83 (m, 1H), 3.52-3.41 (m, 1H), 3.01 (bs, 2H), 1.60 (s, 9H),

25   1.59 (s, 9H), 1.17-1.14 (s, 9H).
LC-MS: R$_t$=4.93 min, m/z: 748.1 [M+H]$^+$

(B):

^{1}H-NMR (300 MHz, CDCl$_3$): δ 12.58-12.52 (s, 1H), 7.60-7.30 (m, 7H), 7.20-7.10 (m, 1H),

30   5.60-5.39 (m, 1H), 5.34 (s, 2H), 4.36-4.02 (m, 2H), 3.86-3.75 (m, 1H), 3.33-3.18 (m, 1H), 2.97-2.90 (m, 1H), 2.83-2.68 (m, 1H), 1.60 (s, 9H), 1.58-1.57 (s, 9H), 1.15-1.09 (s, 9H)
LC-MS: R$_t$=4.93 min, m/z: 748.1 [M+H]$^+$

The above 2-(*tert*-butoxyoxalyl-amino)-5-(4-benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-

35   ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester (50 mg, 0.067 mmol) was dissolved in a mixture of ethyl acetate/ethanol (3 ml, 1:1). Palladium on

58

activated carbon (10 %, 10 mg) was added and the solution degassed and stirred under hydrogen (1 atm.) for 72 hours. TLC analysis indicated that the reaction was incomplete. The mixture was filtered through celite and the filter cake washed with hot ethyl acetate. The filtrate was concentrated in vacuo and purified by silica gel chromatography using a gradient of

5   ethyl acetate/dichloromethane (0 to 5 % gradient) as eluent. Pure fractions were collected and the solvent evaporated in vacuo affording 15 mg (30 %) of 2-(tert-butoxyoxalyl-amino)-5-(4-hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-tert-butyl ester.

¹H-NMR (300 MHz, CDCl₃): δ 12.50 (s, 1H), 7.61-7.51 (m, 1H), 7.39-7.34 (m, 1H),

10   7.17-7.09 (m, 1H), 5.04-4.64 (m, 2H), 4.49-4.34 (m, 1H), 3.90-3.78 (m, 1H), 3.51-3.42 (m, 1H), 3.02 (bs, 2H), 1.60 (s, 18H), 1.17-1.14 (2s, 9H).

The above 2-(tert-butoxyoxalyl-amino)-5-(4-hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-tert-butyl ester (15 mg, 0.023 mmol) was dissolved in a solution of 50 % trifluoroacetic acid/dichloromethane (2 ml).

15   ml). The reaction was stirred at ambient temperature for 12 hours, concentrated in vacuo and evaporated in vacuo from dichloromethane (3 x 10 ml). The resulting precipitate was washed with dichloromethane and dried in vacuo affording 6 mg (47 %) of the title compound as a solid trifluoroacetate.

¹H-NMR (400 MHz, DMSO-d₆): δ 12.32 (s, 1H), 11.17 (s, 1H), 9.25 (bs, 2H), 7.64 (t,

20   1H, J = 8 Hz), 7.32 (d, 1H, J = 8 Hz), 7.24 (d, 1H, J = 8 Hz), 4.41-4.23 (m, 2H), 3.96-3.71 (m, 3H), 3.5-3.2 (obscured by water, 1H), 2.83-2.75 (m, 1H).

LC-MS: Rₜ=1.53 min, m/z: 446.2 [M+H]⁺

25   EXAMPLE 6

7-(4-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

2-(tert-Butoxyoxalyl-amino)-7-(4-benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-

30   4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-tert-butyl ester (50 mg, 0.067 mmol) was dissolved in a mixture of ethyl acetate/ethanol (3 mL, 1:1). Palladium on activated

carbon (10%, 10 mg) was added and the solution degassed and stirred under hydrogen (1 atm) for 72 hours. The mixture was filtered through celite and the filter cake washed with hot ethyl acetate. The filtrate was concentrated in vacuo and the residue purified by silica gel chromatography (10% ethyl acetate/dichloromethane) to obtain 42 mg (95%) of 2-(tert-butoxyoxalyl-amino)-7-(4-hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-tert-butyl ester as an oil.

^{1}H-NMR (400 MHz, CDCl$_3$) δ 12.59-12.53 (2s, 1H), 7.64-7.53 (m, 1H), 7.42-7.36 (m, 1H), 7.19-7.11 (m, 1H), 5.58-5.37 (m, 1H), 4.37-4.00 (m, 2H), 3.86-3.78 (m, 1H), 3.32-3.18 (m, 1H), 2.99-2.94 (m, 1H), 2.84-2.69 (m, 1H), 1.62-1.59 (3s, 18H), 1.17-1.11 (2s, 9H);

LC-MS: R$_t$ = 4.55 min, m/z: 658 [M+H]$^+$,

2-(tert-Butoxyoxalyl-amino)-7-(4-hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-tert-butyl ester (42 mg, 0.064 mmol) was dissolved in a solution of 50% trifluoroacetic acid/methylene chloride (3 mL). The reaction was stirred at ambient temperature for 7 hours, concentrated in vacuo and evaporated from dichloromethane (10 ml) three times. The resulting precipitate was washed with dichloromethane and dried in vacuo to give 29 mg (81 %) of the title compound as a solid trifluoroacetate.

^{1}H-NMR (400 MHz, DMSO-d$_6$) δ 12.32 (bs, 1H), 11.26 (s, 1H), 9.30 (bs, 2H), 7.64 (t, 1H, J = 7 Hz), 7.33 (d, 1H, J = 7 Hz), 7.25 (d, 1H, J = 7 Hz), 4.84 (s, 1H), 4.06-3.96 (m, 2H), 3.56 (m, 2H), 3.05 (bs, 2H),

LC-MS: R$_t$ = 1.26 min, m/z: 446 [M+H]$^+$,

EXAMPLE 7

2-(Oxalyl-amino)-5-(S)-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

2-Methyl-benzoic acid methyl ester (1.50 g 10 mmol), N-bromo-succinimide (1.96 g, 11 mmol) and 2,2'-azobis(2-methyl-propionitrile) (AIBN) (25 mg, 0.15 mmol) were dissolved in chloroform (3 ml). The solution was heated at reflux for 16 hours cooled and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography using a gradient of

ethyl acetate/hexane (1-2 %) as eluent. Pure fractions were collected and the solvent evapo-
rated in vacuo affording 2.05 g (89 %) of 2-bromomethyl-benzoic acid methyl ester as a solid.
^{1}H-NMR (CDCl$_3$): δ 7.97 (d, 1H, J = 7.6 Hz), 7.45-7.52 (m, 2H), 7.38 (dt, 1H, J = 1.2 Hz and J
= 7.6 Hz), 4.96 (s, 2H), 3.95 (s, 1H).

5   To a solution of 2-amino-5-(S)-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester (100 mg, 0.20 mmol)
and pyridine (0.18 ml, 2.0 mmol) in acetonitrile (1 ml) at room temperature was added benzyl
chloroformate (0.28 ml, 2.0 mmol) in 10 aliquots over 48 hours. The solution was then taken
into ethyl acetate (30 ml), washed with 0.5 N hydrochloric acid (3 x 10 ml), saturated sodium

10   bicarbonate (3 x 10 ml), brine (10 ml), dried (MgSO$_4$) and filtered. The solvent was evapora-
ted in vacuo. The resulting oil crystallized upon standing for 2 days. The precipitate was filte-
red off and washed with diethyl ether (3 x 1 ml) affording after drying in vacuo 59 mg (47 %)
of 2-benzyloxy-carbonylamino-5-(S)-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester as a solid.

15   ^{1}H-NMR (CDCl$_3$): δ 10.60 (s, 1H), 7.60-7.92 (m, 4H), 7.38 (m, 5H), 5.26 (s, 2H), 4.30-5.10
(m, 3H), 3.40-4.00 (m, 2H), 1.57 (m, 9H), 1.15 (m, 9H).

         To a solution of 1 N hydrochloric acid in ethyl acetate (1.0 ml) was added 2-
benzyloxy-carbonylamino-5-(S)-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester (52 mg, 0.08 mmol).

20   The solution was stirred at room temperature for 48 hours. A precipitate was filtered off which
afforded 42 mg (90 %) of 2-benzyloxy-carbonylamino-5-(S)-(1,3-dioxo-1,3-dihydro-isoindol-2-
ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester hydrochlo-
ride as a solid.

         ^{1}H-NMR (DMSO-d$_6$): δ 10.45 (s, 1H), 9.40 (s, 1H), 9.25 (s, 1H), 7.89 (m, 4H), 7.39 (m,
25   5H), 5.22 (s, 2H), 4.39 (d, 1H, J = 15 Hz), 4.28 (m, 1H), 3.95 (m, 2H), 3.79 (m, 1H), 3.20 (m,
1H), 2.70 (m, 1H), 1.48 (s, 9H).

         To a solution of the above 2-benzyloxy-carbonylamino-5-(S)-(1,3-dioxo-1,3-dihydro-
isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester
hydrochloride (42 mg, 0.072 mmol) in ethanol (0.5 ml) was added hydrazine (68 μl, 0.22

30   mmol). The solution was stirred at 80 °C for 5 hours and at room temperature for 16 hours.
The mixture was filtered and the filtrate evaporated in vacuo. The residue was extracted with
dichloromethane (5 x 1 ml). The combined dichloromethane washes were evaporated in va-
cuo affording 20 mg (67 %) of 5-(S)-aminomethyl-2-benzyloxy-carbonylamino-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as an oil.

35   ^{1}H-NMR (CDCl$_3$): δ 10.55 (bs, 1H), 7.37 (m, 5H), 5.23 (s, 2H), 3.92 (s, 2H), 2.60-3.10 (m,
3H), 1.53 (s, 9H).

To a solution of the above 5-(S)-aminomethyl-2-benzyloxy-carbonylamino-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (20 mg, 0.048 mmol) in ace-tonitrile (1 ml) at 0 °C was added diisopropylethylamine (18 l, 0.15 mmol) and 2-bromomethyl-benzoic acid methyl (12 mg, 0.048 mmol). The solution was stirred at 0 °C for 3

5   hours and at room temperature for 16 hours. Di-*tert*-butyl dicarbonate (21 mg, 0.096 mmol) was then added to the solution. The solution was then stirred at room temperature for 16 hours. The solution was taken into ethyl acetate (30 ml), washed with 0.5 N hydrochloric acid (3 x 10 ml), saturated sodium bicarbonate (3 x 10 ml) and brine (10 ml), dried (MgSO₄) and filtered. The solvent was evaporated in vacuo. The solid residue was purified by silica gel

10   chromatography using a 5 % mixture of ethyl acetate/hexane as eluent. Pure fractions were collected and the solvent evaporated in vacuo affording 10 mg (33 %) of 2-(benzyloxy-carbonylamino)-5-(S)-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester as a solid.

^{1}H-NMR (CDCl₃): δ 10.59 (s, 1H), 7.81 (m, 1H), 7.52 (m, 1H), 7.39 (m, 7H), 5.25 (s, 1H),

15   4.22-5.00 (m, 4H), 4.40-4.80 (m, 2H), 2.80-3.10 (m, 2H), 1.55 (s, 9H), 1.25 (s, 9H).

To a solution of the above 2-benzyloxycarbonylamino-5-(S)-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester (9 mg, 0.014 mmol) in methanol (2 ml) was added 10 % Pd/C (4 mg). The mixture was stirred under hydrogen (1 atm.) for 3 hours and then filtered. The filtrate was evaporated in

20   vacuo affording 6 mg (93 %) of 2-amino-5-(S)-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester as a solid.

^{1}H-NMR (CDCl₃): δ 7.80 (m, 1H), 7.50 (m, 1H), 7.44 (m, 2H), 4.22-5.00 (m, 4H), 4.40-4.80 (m, 2H), 2.80-3.10 (m, 2H), 1.63 (s, 9H), 1.25 (s, 9H).

To a solution of the above 2-amino-5-(S)-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-

25   4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester (6 mg, 0.013 mmol) in acetonitrile (0.5 ml) at room temperature was added imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (27 mg, 0.13 mmol). The solution was stirred for 3 hours at room temperature and then diluted with ethyl acetate (20 ml), washed with 0.5 N hydrochloric acid (2 x 5 ml), saturated sodium bicarbonate (2 x 5 ml), brine (5 ml), dried (MgSO₄) and filtered. The solvent

30   was evaporated in vacuo. The residue was purified by silica gel chromatography using a gradient of ethyl acetate/hexane (10-25 % gradient) as eluent. Pure fractions were collected and the solvent evaporated in vacuo affording 4 mg (50 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(S)-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester as a solid.

35   ^{1}H-NMR (CDCl₃): δ 12.49 (s, 1H), 7.80 (m, 1H), 7.50 (m, 1H), 7.44 (m, 2H), 4.22-5.00 (m, 4H), 4.20-4.90 (m, 2H), 2.90-3.20 (m, 2H), 1.63 (s, 9H), 1.60 (s, 9H), 1.25 (s, 9H).

To a solution of trifluoroacetic acid/dichloromethane (0.5 ml, 1:1) at room temperature was added the above 2-(*tert*-butoxyoxalyl-amino)-5-(*S*)-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-*tert*-butyl ester (4 mg, 0.006 mmol). The solution was stirred for 3 hours. The solvent was removed in vacuo.
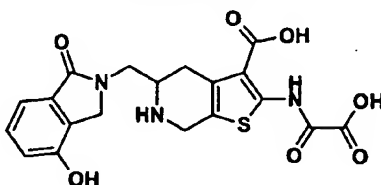5   The residue was washed with dichloromethane affording in quantitative yield the title compound as a solid trifluoroacetate.

^{1}H-NMR (DMSO-d$_6$): δ 12.32 (s, 1H), 4.62 (s, 1H), 4.12 (m, 1H), 3.62-3.78 (m, 2H), 3.40-3.52 (m, 1H), 2.83 (m, 2H).
MS: m/z: 416 [M+H]$^+$.

10

EXAMPLE 8

5-(4-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

15

Acetyl chloride (5.4 ml, 5.96 g, 76 mmol) was added dropwise to methanol (15 ml) at 0 °C in a sealed 50 ml round-bottom flask. This solution was allowed to warm to room temperature for 1 hour while stirring. To this solution 3-hydroxy-2-methyl-benzoic acid (519 mg, 3.4 mmol) was added and the solution was stirred at room temperature for 42 hours. The reaction was
20   quenched with saturated aqueous sodium bicarbonate and solid sodium bicarbonate. The volatiles were removed in vacuo and the basic aqueous solution was then extracted with dichloromethane (4 x 40 ml). The combined organic extracts were dried (MgSO$_4$), filtered, and the solvent evaporated in vacuo affording 493 mg (87 %) of 3-hydroxy-2-methyl-benzoic acid methyl ester as a solid.

25   ^{1}H-NMR (300 MHz, CDCl$_3$): δ 7.43 (d, 1H, *J* = 9 Hz), 7.12 (t, 1H, *J* = 8 Hz), 6.95 (d, 1H, *J* = 8 Hz), 5.05 (bs, 1H), 3.90 (s, 3H), 2.47 (s, 3H).

To a solution of the above methyl ester (256 mg, 1.54 mmol) and N,N-diisopropylethylamine (530 µl, 3.0 mmol) in dichloromethane (8 ml) at 0 °C methyloxymethyl chloride (175 µl, 2.3 mmol) was added dropwise. The solution was allowed slowly to warm to
30   room temperature and stired for 24 hours. The solution was diluted with dichloromethane (12 ml), washed with water (20 ml), brine (20 ml), dried (MgSO$_4$), filtered, and concentrated in vacuo. The resulting oil was purified by silica gel chromatography using a mixture of hexa-

nes/ethyl acetate (4:1) as eluent, which afforded 269 mg (85 %) of 3-methoxymethoxy-2-methyl-benzoic acid methyl ester as an oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ 7.48 (d, 1H, J = 8 Hz), 7.24-7.15 (m, 2H), 5.22 (s, 2H), 3.90 (s, 3H), 3.50 (s, 3H), 2.47 (s, 3H).

5   In a 25 ml round-bottom flask, N-bromo succinimide (236 mg, 1.3 mmol) and azo-bis(cyclohexanecarbonitrile) (33 mg, 0.14 mmol) were added to a solution of 3-methoxymethoxy-2-methyl-benzoic acid methyl ester (265 mg, 1.26 mmol) in carbon tetrachloride (6.5 ml). The reaction was heated to reflux with stirring for 3.5 hours. The volatiles were removed in vacuo and the residue purified by silica gel chromatography using a mixture of

10   hexanes/ethyl acetate (9:1) as eluent, which afforded 364 mg (100 %) of 2-bromomethyl-3-methoxymethoxy-benzoic acid methyl ester as a solid.

^{1}H-NMR (300 MHz, CDCl$_3$): δ 7.55 (dd, 1H, J = 6,3 Hz), 7.29 (d, 2H, J = 3 Hz), 5.27 (s, 2H), 5.05 (s, 2H), 3.91 (s, 3H), 3.50 (s, 3H).

        In a 100 ml round-bottom flask, 2-amino-5-aminomethyl-6-(4-methoxy-benzyl)-

15   4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (298 mg, 0.74 mmol) and N,N-diisopropylethylamine (195 μl, 1.12 mmol) were dissolved in acetonitrile (40 ml). 2-Bromomethyl-3-methoxymethoxy-benzoic acid methyl ester (193 mg, 0.67 mmol) in acetonitrile (5 ml) was slowly added to the amine solution via gastight syringe over 24 hours, followed by stirring at room temperature for an additional 36 hours. The solution was concentra-

20   ted in vacuo, the residue redissolved in ethyl acetate (25 ml), and washed with saturated aqueous sodium bicarbonate (25 ml) and brine (25 ml). The organic phase was dried (MgSO$_4$), filtered, and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography using a mixture of hexanes/ethyl acetate (1:1) as eluent, which afforded 345 mg (81 %) of 2-amino-6-(4-methoxy-benzyl)-5-(4-methoxymethoxy-1-oxo-1,3-dihydro-

25   isoindol-2-ylmethyl)-4,5,6,7-tetrahydro[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as a solid.

        ^{1}H-NMR (300 MHz, CDCl$_3$): δ 7.67 (d, 1H, J = 8 Hz), 7.57-7.38 (m, 5H), 7.14 (d, 2H, J = 8 Hz), 6.96 (m, 2H), 6.77 (d, 2H, J = 9 Hz), 6.20 (d, 2H, J = 6 Hz), 5.96 (s, 2H), 4.69-2.58 (m, 17H), 1.55 (s, 9H).

30   In a 50 ml round-bottom flask a solution of 2-amino-6-(4-methoxy-benzyl)-5-(4-methoxymethoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (338 mg, 0.58 mmol) in dichloromethane (20 ml) was treated with imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (575 mg, 2.9 mmol). After stirring for 18 hours at room temperature, the mixture was concentrated to dryness in vacuo. The residue

35   was purified by silica gel chromatography using a mixture of hexanes/ethyl acetate (1:1) as eluent, which afforded 310 mg (75 %) of 2-(*tert*-Butoxyoxalyl-amino)-6-(4-methoxy-benzyl)-5-

(4-methoxymethoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as a solid.

^{1}H-NMR (300 MHz, CDCl$_3$): δ 12.57 (s, 1H), 7.53 (d, 1H, J = 8 Hz), 7.43 (t, 1H, J = 8 Hz), 7.26 (d, 1H, J = 8 Hz), 7.13 (d, 2H, J = 9 Hz), 6.78 (d, 2H, J = 9 Hz), 5.28 (s, 2H), 4.47 (q,
5   2H, J = 18 Hz), 4.02-3.44 (m, 11H), 2.97 (dd, 1H, J = 18 Hz and J = 5 Hz), 2.76 (dd, 1H, J = 17 Hz and J = 5 Hz), 1.63 (s, 9H), 1.59 (s, 9H).

10 % Pd/C (145 mg, 50 % by weight) was added to a mixture of 2-(*tert*-butoxyoxalyl-amino)-6-(4-methoxy-benzyl)-5-(4-methoxymethoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (283 mg, 0.40 mmol)
10   in 10 % formic acid and methanol (10 ml). After stirring at room temperature for 18 hours, more Pd/C (141 mg, 50 % by weight) was added to the reaction mixture. After stirring at room temperature for an additional 20 hours, the catalyst was removed via fitration through celite. Fresh Pd/C (255 mg) and ammonium formate (1.0 g) were added to the residue (253 mg, 0.36 mmol) dissolved in 10 % formic acid in methanol (10 ml). The solution was heated
15   to 40 °C for 48 hours. Catalyst was removed via filtration through celite and liberal washing with methanol. Purification by chromatotron (ethyl acetate/triethylamine (99:1)) afforded 63 mg (27 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(4-methoxymethoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester **A** and 46 mg (19 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(4-methoxymethoxy-1-oxo-1,3-dihydro-isoindol-2-
20   ylmethyl)-6-methyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester **B**.

A: ^{1}H-NMR (300 MHz, CDCl$_3$): δ 12.54 (s, 1H), 7.50 (d, 1H, J = 8 Hz), 7.41 (t, 1H, J = 8 Hz), 7.25 (d, 1H, J = 8 Hz), 5.27 (s, 2H), 4.52 (dd, 2H, J = 30 Hz and J = 19 Hz), 4.08-3.90 (m,
25   2H), 3.86-3.67 (m, 2H), 3.51 (s, 3H), 3.27 (m, 1H), 2.99 (dd, 1H, J = 18 Hz and J = 4 Hz), 2.53 (dd, 1H, J =18 Hz and J = 11 Hz), 1.61 (s, 9H), 1.53 (s, 9H).
LC-MS (APCl$^+$) m/z: 588 [M+H]$^+$; R$_t$ = 1.32 min.

B: ^{1}H-NMR (300 MHz, CDCl$_3$): δ 12.56 (s, 1H), 7.50 (d, 1H, J = 7 Hz), 7.41 (t, 1H, J = 8 Hz),
30   7.25 (d, 1H, J = 8 Hz), 5.27 (s, 2H), 4.50 (dd, J = 28 Hz and J = 18 Hz), 3.93-3.68 (m, 4H), 3.51 (s, 1H), 3.51 (s, 3H), 3.31 (m, 1H), 2.88 (dd, 1H, J = 18 Hz and J = 4 Hz), 2.68 (dd, 1H, J =19 Hz and J = 9 Hz), 2.46 (s, 3H), 1.61 (s, 9H), 1.54 (s, 9H).
LC-MS (APCl$^+$) m/z: 602 [M+H]$^+$; R$_t$ = 1.35 min.

35   2-(*tert*-Butoxyoxalyl-amino)-5-(4-methoxymethoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester **A** (63 mg, 0.11

mmol) was dissolved in 30 % trifluoroacetic acid in dichloromethane (4 ml). The solution was left open to the atmosphere without stirring. After 24 hours the precipitate was filtered off and washed with diethyl ether, affording 57 mg (90 %) of the title compound as a solid trifluoroacetate.

5   ^{1}H-NMR (300 MHz, DMSO-d$_6$): δ 12.30 (s, 1H), 10.17 (s, 1H), 9.23 (s, 2H, J = 5 Hz and J = 7 Hz), 7.34 (t, 1H, J = 6 Hz), 7.19 (d, 1H, J = 5 Hz), 7.03 (d, 1H, J = 6 Hz), 5.76 (s, 2H), 4.53 (d, 1H, J = 13 Hz), 4.43-4.22 (m, 3H), 4.07 (m, 1H), 3.91 (m, 1H), 3.70 (m, 1H), 3.10 (m, 1H), 2.82 (dd, 1H, J = 14 Hz and J = 8 Hz).

10

EXAMPLE 9

5-(4-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-methyl-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

15

The above 2-(tert-butoxyoxalyl-amino)-5-(4-methoxymethoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-methyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester B (46 mg, 0.08 mmol) was dissolved in 30 % trifluoroacetic acid in dichloromethane (4 ml). The solution was left open to the atmosphere without stirring. After 24 hours the precipitate was

20   filtered off and washed with diethyl ether, affording 41 mg (90 %) of the title compound as a solid trifluoroacetate.

^{1}H-NMR (400 MHz, CDCl$_3$): δ 12.39 (s, 1H), 10.19 (s, 1H), 10.10 (s, 1H), 7.32 (t, 1H, J = 7.6 Hz), 7.17 (d, 1H, J = 7.2 Hz), 7.02 (t, 1H, J = 7.2 Hz), 4.55 (d, 2H, J = 15 Hz), 4.0-4.5 (m, 4H), 2.95-3.70 (m, 5H), 2.85 (s, 3H).

25   LC-MS (APCI$^+$) m/z: 446 [M+H]$^+$; R$_t$ = 1.02 min.

EXAMPLE 10

5-((1,1-Dioxo-1H-benzo[d]isothiazol-3-ylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-
thieno[2,3-c]pyridine-3-carboxylic acid

Saccharin (8.8 g, 48 mmol) and phosphorous pentachloride (15 g, 72 mmol) were added
neat to a round bottom flask equipped with a short path distillation column. The mixture was
5   heated to 175 °C. After approximately 0.5 hour, phosphorous oxychloride slowly distilled off.
Upon completion of the reaction, the mixture was cooled and the resultant solid recrystallized
from benzene affording 3.6 g (37 %) of 3-chloro-benzo[d]isothiazole 1,1-dioxide as a solid.
^{1}H-NMR (CDCl$_3$): δ 7.92 (d, 1H, J = 6.9 Hz), 7.8 (m, 3H).

To a solution of 2-amino-5-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-
10   thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester (155 mg, 0.384 mmol) and triethylami-
ne (59 μl, 0.423 mmol) in dichloromethane (2 ml) at 0 °C, was added a solution of 3-chloro-
benzo[d]isothiazole 1,1-dioxide (85.2 mg, 0.423 mmol) in dichloromethane (2 ml). The reac-
tion mixture was stirred at 0 °C for 1hour. The reaction was judged complete by tlc (dichloro-
methane/ethyl acetate (1:1)). The reaction mixture was washed with water (3 x 20 ml), dried
15   (MgSO$_4$), filtered and the solvent evaporated in vacuo. The crude residue was subjected to
flash chromatography using a gradient from 100 % dichloromethane to dichlorometha-
ne/ethyl acetate (80/20) as eluent, which afforded 200 mg (92 %) of 2-amino-5-((1,1-dioxo-
1H-benzo[d]isothiazol-3-ylamino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-
c]pyridine-3-carboxylic acid tert-butyl ester as a foam.

20   ^{1}H-NMR (CD$_3$OD): δ 7.99 (m, 1H), 7.87 (m, 1H), 7.79 (m, 2H), 7.19 (d, 2H, J = 8.4
Hz), 6.75 (d, 2H, J = 8.7 Hz), 3.88-3.79 (m, 2H), 3.75-3.59 (m, 3H), 3.69 (s, 3H), 3.52-3.46
(m, 2H), 2.84 (dd, 1H, J = 15.3 Hz and J = 5.4 Hz), 2.68 (dd, J = 18 Hz and J = 4.5 Hz), 1.46
(s, 9H).

LC-MS: R$_t$ = 2.83, m/z: 569 [M+H]$^+$

25   To a solution of 2-amino-5-((1,1-dioxo-1H-benzo[d]isothiazol-3-ylamino)-methyl)-6-(4-
methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester
(129 mg, 0.227 mmol) in tetrahydrofuran (3 ml) was added imidazol-1-yl-oxo-acetic acid tert-
butyl ester (1.1 ml, 1.1 mmol, 1 M in tetrahydrofuran). The reaction mixture was stirred at
room temperature for 18 hours. The reaction mixture was concentrated in vacuo and the re-
30   sidue subjected to flash chromtography using a mixture of ethyl acetate/dichloromethane
(10:90) as eluent, which afforded 142 mg (90%) of 2-(tert-butoxyoxalyl-amino)-5-((1,1-dioxo-
1H-benzo[d]isothiazol-3-ylamino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-
c]pyridine-3-carboxylic acid tert-butyl ester as an oil.

^{1}H-NMR (CDCl$_3$): δ 7.92 (d, 1H, J = 6.3 Hz), 7.73 (m, 2H), 7.56 (d, 1H, J = 5.7 Hz),
35   7.20 (d, 2H, J = 6.3 Hz), 7.05 (bs, 1H), 6.87 (d, 2H, J = 6.6 Hz), 3.91 (m, 2H), 3.82-3.72 (m,

2H), 3.79 (s, 3H), 3.61-3.49 (m, 2H), 3.44 (m, 1H), 3.11 (dd, 1H, J = 15 Hz and J = 3.6 Hz),
2.72 (dd, 1H, J = 12 Hz and J = 4.2 Hz), 1.63 (s, 18H);

LC-MS: R$_t$=3.48, m/z: 697 [M+H]$^+$

2-(*tert*-Butoxyoxalyl-amino)-5-((1,1-dioxo-1*H*-benzo[d]isothiazol-3-ylamino)-methyl)-6-
(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester
(120 mg, 0.172 mmol) was dissolved in a mixture of ethanol (4 ml) and formic acid (0.5 ml).
10 % Pd-C (20 mg) was added and the reaction mixture stirred at ambient temperature for 4
days (after the second day, 150 mg of additional 10 % Pd-C was added). The reaction mix-
ture was filtered through celite and the celite washed with dichloromethane. The organic frac-
tions were combined and concentrated in vacuo. The resultant oil was subjected to prepara-
tive thin layer chromatography (dichloromethane/methanol (95:5)), which afforded 17 mg (17
%) of 2-(*tert*-butoxyoxalyl-amino)-5-((1,1-dioxo-1H-benzo[d]isothiazol-3-ylamino)-methyl)-
4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as a solid.

^{1}H-NMR (CDCl$_3$): δ 7.91 (m, 1H), 7.72 (m, 3H), 7.34 (bs, 1H), 4.16-4.08 (m, 1H), 4.07 (dd,
2H, J = 36.3 Hz and J = 8.7 Hz), 3.38-3.30 (m, 1H), 3.22-3.06 (m, 2H), 2.51 (dd, 1H, J = 16.8
Hz and J = 9.9 Hz), 1.61 (s, 18H).
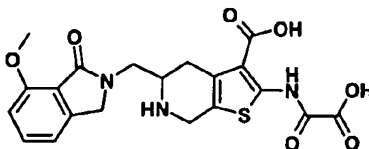
2-(*tert*-Butoxyoxalyl-amino)-5-((1,1-dioxo-1H-benzo[d]isothiazol-3-ylamino)-methyl)-
4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (15 mg, 0.026 mmol)
was dissolved in a solution of 50 % trifluoroacetic acid/dichloromethane (3 ml). The reaction
mixture was stirred at ambient temperature for 18 hours, concentrated in vacuo and re-
evaporated from acetonitrile (2x). The residue was washed with dichloromethane and dried
in vacuo to give 16 mg (90 %) of the title compound as a solid trifluoroacetate.

^{1}H-NMR (CD$_3$OD): δ 7.98 (d, 1H, J = 7.2 Hz), 7.92 (d, 1H, J = 6.6 Hz), 7.83 (m, 2H), 4.51-
4.39 (m, 2H), 4.11-4.08 (m, 1H), 3.97-3.91 (m, 2H), 3.53-3.47 (m, 1H), 3.16-3.10 (m, 1H).

EXAMPLE 11

7-((1,1-Dioxo-1H-benzo[d]isothiazol-3-ylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-
thieno[2,3-c]pyridine-3-carboxylic acid

68

3-Chloro-benzo[d]isothiazole-1,1-dioxide (160 mg, 0.79 mmol) and diisopropylethylamine
(150 µl, 0.86 mmol) were dissolved in dichloromethane (7 ml) at 0 °C. 2-Amino-7-
aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid
tert-butyl ester (284 mg, 0.70 mmol) was added and the mixture was stirred for 15 minutes at

5   0 °C, diluted with dichloromethane (10 ml) and washed with water (20 ml) and brine (20 ml).
The organic phase was dried (MgSO₄), filtered, and the solvent evaporated <u>in vacuo</u>. The
residue was purified by silica gel chromatography using a gradient of hexanes/ethyl acetate
(1:1) to pure ethyl acetate as eluent, which afforded 309 mg (77 %) of 2-amino-7-((1,1-dioxo-
1*H*-benzo[d]isothiazol-3-ylamino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-

10   c]pyridine-3-carboxylic acid *tert*-butyl ester as an foam.

       ¹H-NMR (300 MHz, CDCl₃): δ 7.89 (d, 1H, J = 8 Hz), 7.77-7.63 (m, 2H), 7.37 (d, 1H, J
= 7 Hz), 7.25 (d, 2H, J = 10 Hz), 6.82 (d, 2H, J = 8 Hz), 6.62 (bs, 1H), 6.08 (s, 2H), 3.91 (m,
1H), 3.71 (s, 3H), 3.49-2.65 (m, 8H), 1.59 (s, 9H).
       LC-MS (APCl⁺) m/z: 569 [M+H]⁺, [M+Na] 591; Rₜ = 2.85 min.

15   2-Amino-7-((1,1-dioxo-1*H*-benzo[d]isothiazol-3-ylamino)methyl)-6-(4-methoxy-
benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (102 mg,
0.18 mmol) in dichloromethane (10 ml) was treated with imidazol-1-yl-oxo-acetic acid *tert*-
butyl ester (85 mg, 0.43 mmol). After stirring for 18 hours at room temperature, the reaction
solution was concentrated to dryness <u>in vacuo</u>. The residue was purified by silica gel chro-

20   matography using a gradient of hexanes/ethyl acetate (1:1) to pure ethyl acetate as gradient,
which afforded 98 mg (78 %) of 2-(*tert*-butoxyoxalyl-amino)-7-((1,1-dioxo-1*H*-
benzo[d]isothiazol-3-ylamino)-methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-
c]pyridine-3-carboxylic acid *tert*-butyl ester as a solid.

       ¹H-NMR (300 MHz, CDCl₃): δ 12.57 (s, 1H), 7.89 (d, 1H, J = 8 Hz), 7.77-7.63 (m, 2H),

25   7.39 (d, 1H, J = 7 Hz), 7.25 (d, 2H, J = 9 Hz), 6.84 (d, 2H, J = 9 Hz), 6.64 (bs, 1H), 3.99-2.76
(m, 12H), 1.64 (s, 9H), 1.63 (s, 9H).

       10 % Pd/C (100 mg) was added to a mixture of 2-(*tert*-butoxyoxalyl-amino)-7-((1,1-
dioxo-1*H*-benzo[d]isothiazol-3-ylamino)-methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-
thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (98 mg, 0.14 mmol) in 10 % formic acid

30   in methanol (10 ml). After stirring at room temperature for 48 hours, the catalyst was remo-
ved via filtration through celite and liberal washing with methanol. The volatiles were remo-
ved <u>in vacuo</u> and the residue purified by chromatotron (ethyl acetate/triethylamine, 99:1),
which afforded 32 mg (40 %) of 2-(*tert*-butoxyoxalyl-amino)-7-((1,1-dioxo-1*H*-
benzo[d]isothiazol-3-ylamino)-methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic

35   acid *tert*-butyl ester as an oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ 12.48 (s, 1H), 10.21-9.15 (m, 2H), 8.49-7.42 (m, 3H), 5.62-5.00 (bs, 1H), 4.53-2.87 (m, 8H), 1.61 (s, 18H).

HPLC (254.4 nm) R$_t$ = 3.67 minutes.

2-(*tert*-Butoxyoxalyl-amino)-7-((1,1-dioxo-1*H*-benzo[d]isothiazol-3-ylamino)-methyl)-
4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (32 mg) was dissol-
ved in a mixture of 30 % trifluoroacetic acid in dichloromethane (4 ml). The solution was left
open to the atmosphere without stirring. After 24 hours the precipitate was filtered off and
washed with diethyl ether, affording 29 mg (90 %) of the title compound as a solid trifluoroa-
cetate.

^{1}H-NMR (300 MHz, DMSO-d$_6$): δ 12.36 (s, 1H), 9.92 (bs, 1H), 9.73 (bs, 1H), 9.38 (bs,
1H), 8.20 (m, 1H), 8.05 (m, 1H), 7.89 (m, 2H), 4.95 (s, 1H), 4.12-3.00 (m partially obscured
by water, 8H).

LC-MS (APCl$^+$) m/z: 466 [M+H]$^+$; R$_t$ = 0.66 min.

EXAMPLE 12

5-(7-Methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-
thieno[2,3-c]pyridine-3-carboxylic acid

2-Methoxy-6-methylbenzoic acid ethyl ester (500 mg, 2.67 mmol), N-bromosuccinimide
(483.8 mg, 2.72 mmol) and 2,2'-azobis(2-methyl-propionitrile) (30.2 mg, 0.123 mmol) in car-
bon tetrachloride (10 ml) were heated to reflux. After 18 hours, the reaction mixture was
evaporated to dryness in vacuo. The residue was dissolved in dichloromethane (100 ml) and
washed with water (2 x 50 ml). The organic layer was dried (MgSO$_4$), filtered and the solvent
evaporated in vacuo. The residue (702 mg) was purified by column chromatography using a
mixture of hexanes/dichloromethane (1:1) as eluent, which afforded 573 mg (85 %) of 6-
bromomethyl-2-methoxy-benzoic acid ethyl ester as an oil.

^{1}H-NMR (CDCl$_3$): δ 7.37 (t, 1H, J = 8.4 Hz), 7.01 (d, 1H, J = 8.1 Hz), 6.90 (d, 1H, J =
8.4 Hz), 4.54 (s, 2H), 4.45 (q, 2H, J = 7.2 Hz), 3.82 (s, 3H), 1.42 (t, 3H, J = 9 Hz).

6-Bromomethyl-2-methoxy-benzoic acid ethyl ester (71.1 mg, 0.260 mmol) dissolved
in acetonitrile (5 ml) and diisopropylethylamine (453 µl, 2.60 mmol) was stirred at room tem-
perature. To this mixture 2-amino-5-amino-methyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-

thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (200 mg, 0.52 mmol) dissolved in ace-
tonitrile (5 ml) was added syringe pump (0.2 ml/min.). Once addition was complete, the reac-
tion mixture was allowed to stir for 2 hours. The reaction mixture was concentrated in vacuo,
and the residue diluted with ethylacetate (50 ml). The organic layer was washed with satura-
5   ted sodium bicarbonate (2 x 25 ml) and brine (2 x 25 ml). The organic layer was dried
(MgSO₄), filtered and concentrated in vacuo. The residue (308 mg) was subjected to column
chromatography using a gradient of hexane/ethyl acetate (95:5) to (50:50) and then dichlo-
romethane/ethyl acetate (95:5) as eluents, which afforded 106 mg (75 %) of 2-amino-6-(4-
methoxy-benzyl)-5-(7-methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-
10   thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H-NMR (CDCl₃): δ 7.48 (t, 1H, J = 7.5 Hz), 7.12 (d, 2H, J = 8.4 Hz), 7.01 (d, 1H, J =
7.5 Hz), 6.91 (d, 1H, J = 8.4 Hz), 6.76 (d, 2H, J = 7.8 Hz), 5.95 (bs, 2H), 4.37 (s, 2H), 4.05
(m, 1H), 3.97 (s, 3H), 3.88-3.78 (m, 2H), 3.81 (s, 3H), 3.71-3.39 (m, 4H), 2.90 (dd, 1H, J = 18
Hz and J = 5.4 Hz), 2.62 (dd, 1H, J = 18 Hz and J = 5.4 Hz), 1.53 (s, 9H).

15   To a solution of 2-amino-6-(4-methoxy-benzyl)-5-(7-methoxy-1-oxo-1,3-dihydro-
isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester
(105 mg, 0.192 mmol) in tetrahydrofuran (3 ml) was added imidazol-1-yl-oxo-acetic acid *tert*-
butyl ester (0.534 ml, 0.534 mmol, 1 M in tetrahydrofuran). The reaction mixture was stirred
at room temperature for 18 hours. The reaction mixture concentrated in vacuo and the resi-
20   due subjected to flash chromtography using a mixture of ethyl acetate/dichloromethane
(10:90) as eluent, which afforded 85 mg (66 %) of 2-(*tert*-butoxyoxalyl-amino)-6-(4-methoxy-
benzyl)-5-(7-methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-
c]pyridine-3-carboxylic acid *tert*-butyl ester.

^{1}H-NMR (CDCl₃): δ 7.47 (t, 1H, J = 5.7 Hz), 7.10 (d, 2H, J = 6 Hz), 6.99 (d, 1H, J = 5.7
25   Hz), 6.90 (d, 1H, J = 6.3 Hz), 6.76 (d, 2H, J = 6.3 Hz), 4.37 (q, 2H, J = 11.4 Hz), 3.99-3.92
(m, 1H), 3.97 (s, 3H), 3.79-3.76 (m, 2H), 3.77 (s, 3H), 3.66 (d, 1H, J = 12.6 Hz), 3.58-3.50
(m, 3H), 2.95 (dd, 1H, J = 13.5 Hz and J = 3.6 Hz), 2.70 (dd, 1H, J = 13.5 Hz and J = 3.6 Hz),
1.61 (d, 9H), 1.57 (s, 9H).

            2-(*tert*-Butoxyoxalyl-amino)-6-(4-methoxy-benzyl)-5-(7-methoxy-1-oxo-1,3-dihydro-
30   isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester
(66 mg, 0.12 mmol) was dissolved in ethanol (2 ml) and formic acid (0.3 ml). 10 % Pd-C (15
mg) was added and the reaction mixture stirred at room temperature for 3 days. TLC (hexa-
ne/ethyl acetate (1/1)) indicated reaction complete. The reaction mixture was filtered through
celite and the celite washed with dichloromethane. The organic fractions were combined and
35   subjected to preparative thin layer chromatography (hexane/ethyl acetate (1/1) to yield 14.7

mg (22 %) of 2-(tert-butoxyoxalyl-amino)-5-(7-methoxy-1-oxo-1,3-dihydro-isoindol-2-
ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester as an oil.

^{1}H-NMR (CDCl$_3$): δ 7.48 (t, 1H, J = 7.5 Hz), 7.01 (d, 1H, J = 7.2 Hz), 6.90 (d, 1H, J =
8.4 Hz), 5.50 (d, 2H, J = 6.6 Hz), 4.04-3.90 (m, 1H), 3.97 (s, 3H), 3.24 (m, 1H), 3.01-2.95 (m,
5   1H), 2.57-2.43 (m, 2H), 1.62 (s, 9H), 1.57 (s, 9H).

2-(tert-Butoxyoxalyl-amino)-5-(7-methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-
4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester (14.7 mg, 0.026
mmol) was dissolved in a solution of 50% trifluoroacetic acid/dichloromethane (2 ml). The
reaction mixture was stirred at ambient temperature for 18 hours, concentrated in vacuo and
10 re-evaporated from acetonitrile (2x). The resulting precipitate was washed with dichloro-
methane and dried in vacuo to give 13 mg (89 %) of the title compound as a solid trifluoroa-
cetate.

^{1}H-NMR (CD$_3$OD): δ 7.56 (t, 1H, J = 8.1 Hz), 7.13 (d, 1H, J = 7.2 Hz), 7.01 (d, 1H, J =
8.1 Hz), 4.87-4.44 (m, 4H), 4.15 (m, 1H), 3.90 (s, 3H), 3.88-3.79 (m, 1H), 3.43 (m, 1H), 2.98
15 (m, 2H);
LC-MS: R$_t$ = 0.71, m/z: 446 [M+H]$^+$.

EXAMPLE 13

20

5-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-
thieno[2,3-c]pyridine-3-carboxylic acid

25 To a solution of 2-hydroxy-6-methyl-benzoic acid ethyl ester (5.00 g, 27.8 mmol) and t-butyl-
di-methylsilyl chloride (6.27 g, 41.6 mmol) in dichloromethane (100 ml) was added diisopro-
pyl ethylamine. The solution was stirred at 50 °C for 24 hours, washed with water, brine,
dried (MgSO$_4$), filtered and the solvent evaporated in vacuo, which afforded 7.6 g (93 %) of
2-(tert-butyl-dimethyl-silanyloxy)-6-methyl-benzoic acid ethyl ester as an oil.
30 ^{1}H-NMR (CDCl$_3$): δ 7.13 (t, 1H, J = 7.5 Hz), 6.78 (d, 1H, J = 7.5 Hz), 6.67 (d, 1H, J = 7.5 Hz),
4.35 (q, 2H, J = 7.2 Hz), 2.29 (s, 3H), 1.38 (t, 3H, J = 7.2 Hz), 0.97 (s, 9H), 0.23 (s, 6H).

2-(tert-Butyl-dimethyl-silanyloxy)-6-methyl-benzoic acid ethyl ester (7.6 g, 25.8
mmol), N-bromosuccinimide (4.82 g, 27.1 mmol) and azobis(cyclohexanecarbonitrile) (0.32
g, 1.3 mmol) were dissolved in tetrachlormethane (130 ml). The solution was stirred at room
35 temperature for 60 hours. The solvent was evaporated in vacuo and the residue was chro-

matographed on silica gel column using a gradient of 1-2% ethyl acetate/hexane as eluent, which afforded 8.0 g (83 %) of 6-bromomethyl-2-(*tert*-butyl-dimethyl-silanyloxy)-benzoic acid ethyl ester as an oil.

   ^{1}H-NMR (CDCl$_3$): δ 7.21 (t, 1H, J = 8.4 Hz), 7.00 (d, 1H, J = 8.4 Hz), 6.81 (d, 1H, J = 8.4 Hz), 4.51 (s, 2H), 4.40 (q, 2H, J = 7.2 Hz), 1.42 (t, 3H, J = 7.2 Hz), 0.98 (s, 9H), 0.23 (s, 6H).

   To a solution of 2-amino-5-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (3.00 g, 7.45 mmol) and diisopropyl ethylamine (1.93 ml, 11.2 mmol) in acetonitrile at room temperature was added a solution of 6-bromomethyl-2-(*tert*-butyl-dimethyl-silanyloxy)-benzoic acid ethyl ester (2.78 g, 7.45 mmol) in acetonitril over 48 hours. The solution was stirred for 12 hours after the addition was complete. The volatiles were evaporated in vacuo and the residue was taken into ethyl acetate (50 ml) and washed with water, 1 N hydrochloric acid, brine, dried (MgSO$_4$), filtered and the solvent evaporated in vacuo. The residue was chromatographed on silica gel column eluted with a mixture of 20 % ethyl acetate/Hexane, which afforded 3.2 g (66 %) of 2-amino-5-(7-(*tert*-butyl-dimethyl-silanyloxy)-1-oxo-1,3-dihydro-isoindol-2-ylmethyl]-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as an oil.

   ^{1}H-NMR (CDCl$_3$): δ 7.36 (t, 1H, J = 8.0 Hz), 7.11 (d, 2H, J = 8.8 Hz), 6.99 (d, 1H, J = 8.0 Hz), 6.82 (d, 1H, J = 8.0 Hz), 6.76 (d, 2H, J = 8.8 Hz), 5.94 (s, 2H), 4.48 (d, 1H, J = 16.8 Hz), 4.33 (d, 1H, J = 16.8 Hz), 3.90-3.45 (m, 7H), 3.78 (s, 3H), 2.95 (dd, 1H, J = 17.2 Hz and J = 5.2 Hz), 2.72 (dd, 1H, J = 17 Hz and J = 5.6 Hz), 1.52 (s, 9H), 1.05 (s, 9H), 0.26 (s, 6H).

   To a stirred solution of 2-amino-5-(7-(*tert*-butyl-dimethyl-silanyloxy)-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (2.37 g, 3.64 mmol) in tetrahydrofuran (50 ml) was added imi-dazol-1-yl-oxo-acetic acid *tert*-butyl ester (2.14 mg, 10.9 mmol) in tetrahydrofuran (10 ml). The mixture was stirred at room temperature for 24 hours. The solvent was removed in vacuo. The residue was taken into ethyl acetate (100 ml). The solution was washed with 0.5 N hydrochloric acid solution (2 x 20 ml), saturated sodium bicarbonate (2 x 20 ml) and brine (20 ml), dried (MgSO$_4$), filtered and the solvent removed in vacuo. The residue was chroma-tographed using a gradient of 10-20 % ethyl acetate/Hexane as eluent, which afforded 2.40 g (92 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(7-(*tert*-butyl-dimethyl-silanyloxy)-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as a solid.

   ^{1}H-NMR (CDCl$_3$): δ 12.59 (s, 1H), 7.37 (t, 1H, J = 8.0 Hz), 7.10 (d, 2H, J = 8.8 Hz), 7.00 (d, 1H, J = 8.0 Hz), 6.83 (d, 1H, J = 8.0 Hz), 6.77 (d, 2H, J = 8.8 Hz), 4.50 (d, 1H, J = 16.8 Hz), 4.34 (d, 1H, J = 16.8 Hz), 3.90-3.45 (m, 7H), 3.77 (s, 3H), 2.95 (dd, 1H, J = 17.2 Hz

73

and J = 5.2 Hz), 2.72 (dd, 1H, J = 18 and J = 5.6 Hz), 1.61 (s, 9H), 1.58 (s, 9H), 1.06 (s, 9H), 0.26 (s, 6H).

5   To a solution of 2-(tert-butoxyoxalyl-amino)-5-(7-(tert-butyl-dimethyl-silanyloxy)-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester (2.40 g, 3.34 mmol) in 10 % formic acid/methanol (50 ml) at room temperature under nitrogen was added 10 % Pd/C (1.2 g). The mixture was stirred for 48 hours. The Pd/C was filtered off and the filtrate was evaporated in vacuo. The residue was dissolved in dichloromethane (10 ml). The resulting solution was poured into hexane. The precipitate was filtered off and dried in vacuo affording 1.3 g (61 %) of 2-(tert-

10   butoxyoxalyl-amino)-5-(7-(tert-butyl-dimethyl-silanyloxy)-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester.

^{1}H-NMR (CDCl$_3$): δ 12.45 (s, 1H), 8.05 (s, 1H), 7.39 (t, 1H, J = 8.0 Hz), 7.00 (d, 1H, J = 8.0 Hz), 6.83 (d, 1H, J = 8.0 Hz), 4.50 (d, 1H, J = 16.8 Hz), 4.45 (q, 2H, J = 17 Hz), 4.05 (q, 2H, J = 17 Hz), 3.82 (dd, 1H, J = 17.2 Hz and J = 5.2 Hz), 3.72 (dd, 1H, J = 17 Hz and J =

15   5.6 Hz), 3.40 (s, 1H), 3.08 (d, 1H, J = 17 Hz), 2.61 (dd, 1H, J = 18 Hz and J = 7.2 Hz), 1.61 (s, 9H), 1.54 (s, 9H), 1.05 (s, 9H), 0.26 (s, 6H).

To a solution of trifluoroacetic acid (33.3 ml) and H$_2$O (2.7 ml) was added 2-(tert-butoxyoxalyl-amino)-5-(7-(tert-butyl-dimethyl-silanyloxy)-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester (0.70 g,

20   1.04 mmol). The solution was stirred at room temperature for 40 hours. The solvent was poured into ethyl ether (400 ml). The precipitate was filtered off and dried in vacuo, which afforded 450 mg (80 %) of the title compound as a solid trifluoroacetate.

^{1}H-NMR (DMSO-d$_6$): δ 12.30 (s, 1H), 9.71 (s, 1H), 9.20 (s, 2H), 7.39 (t, 1H, J = 8.0 Hz), 6.99 (d, 1H, J = 8.0 Hz), 6.82 (d, 1H, J = 8.0 Hz), 4.52 (d, 1H, J = 16.8 Hz), 4.36 (d, 2H, J = 17

25   Hz), 4.22 (d, 2H, J = 17 Hz), 4.00 (dd, 1H, J = 17.2 Hz and J = 5.2 Hz), 3.86 (s, 1H), 3.62 (d, 1H, J = 17 Hz), 2.81 (dd, 1H, J = 18 Hz and J = 7.2 Hz);

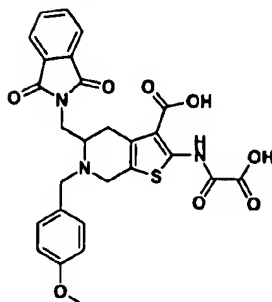LC-MS: R$_t$ = 1.20 min; m/z = 432 [M+H]$^+$

EXAMPLE 14

30

5-(7-Benzyloxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

74

To a solution of 2-(*tert*-butoxyoxalyl-amino)-5-(7-(*tert*-butyl-dimethyl-silanyloxy)-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (2.40 g, 3.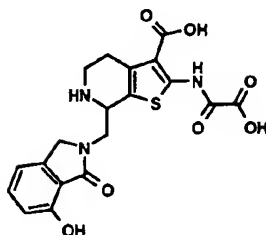34 mmol) in 10 % formic acid/methanol (50 ml) at room temperature under nitrogen was added 10 % Pd/C (1.2 g). The mixture was stirred for

5   48 hours. The Pd/C was filtered off and the filtrate was evaporated in vacuo. The residue was dissolved in dichloromethane (10 ml) and the resulting solution was poured into hexane. The precipitate was filtered off (1.3 g) and the filtrate was evaporated in vacuo. The residual foam (1.1 g) was taken into dichloromethane (50 ml) and treated with di-*tert*-butyl-dicarbonate (1.1 g, 5.0 mmol) and saturated sodium bicarbonate (20 ml). The mixture was

10   stirred for 2 hours and the organic layer was separated and dried (MgSO$_4$). The solvent was evaporated in vacuo and the residue was chromatographed using a gradient of 10-30% ethyl acetate/Hexane as eluent, which afforded 175 mg of 2-(*tert*-butoxyoxalyl-amino)-5-(7-hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyridine-3,6-carboxylic acid di-*tert*-butyl ester.

15   ^{1}H-NMR (CDCl$_3$): δ 12.55 (s, 1H), 8.53 (s, 1H), 7.37 (t, 1H, J = 7.6 Hz), 6.92 (d, 1H, J = 7.6 Hz), 6.83 (d, 1H, J = 7.6 Hz), 4.95 (s, 1H), 4.84 (d, 1H, J = 16.4 Hz), 4.72 (d, 1H, J = 16.0 Hz), 4.56 (d, 1H, J = 16.0 Hz), 4.28 (d, 1H, J = 17.6 Hz), 4.13 (m, 1H), 3.68 (s, 0.5H), 3.42 (s, 0.5H), 3.16-2.94 (m, 2H), 1.62 (s, 9H), 1.61 (s, 9H), 1.26 (s, 9H).

           To a solution of 2-(*tert*-butoxyoxalyl-amino)-5-(7-hydroxy-1-oxo-1,3-dihydro-isoindol-

20   2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyridine-3,6-carboxylic acid di-*tert*-butyl ester (16 mg, 0.025 mmol) in N,N-dimethylformamide (0.5 ml) under nitrogen was added sodium hydride (1.0 mg, 0.026 mmol) at room temperature. The solution was stirred for 2 hours and followed by addition of benzyl bromide (5.9 ml, 0.050 mmol). The solution was stirred for 16 hours, diluted with ethyl acetate (20 ml) and washed with 0.5 N hydrochloric acid solution (2

25   x 10 ml), saturated sodium bicarbonate (2 x 10 ml), brine (10 ml), dried (MgSO$_4$), and filtered. The solvent was removed in vacuo. The residue was chromatographed using a gradient of 10-20 % ethyl acetate/Hexane as eluent, which afforded 14 mg (76 %) of 5-(7-benzyloxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyridine-3,6-carboxylic acid di-*tert*-butyl ester as a solid.

30   ^{1}H-NMR (CDCl$_3$): δ 12.49 (s, 1H), 7.48 (d, 2H, J = 7.2 Hz), 7.35 (m, 3H), 7.28 (d, 1H, J = 7.2 Hz), 6.97 (d, 1H, J = 7.6 Hz), 6.80 (d, 1H, J = 7.6 Hz), 5.32 (s, 2H), 4.97 (m, 2H), 4.82-4.62 (m, 2H), 4.45-4.15 (m, 2H), 3.68 (s, 0.5H), 3.48 (s, 0.5H), 3.16-2.94 (m, 2H), 1.62 (s, 9H), 1.60 (s, 9H), 1.26 (s, 9H).

           To a solution of trifluoroacetic acid (0.5 ml) and dichloromethane (2.7 ml) was added

35   5-(7-benzyloxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyridine-3,6-carboxylic acid di-*tert*-butyl ester (14 mg, 0.019 mmol).

The solution was stirred at room temperature for 40 hours. The reaction mixture was poured into ethyl ether (20 ml). The precipitate was filtered off and dried in vacuo affording 8.0 mg (68 %) of the title compound as a solid trifluoroacetate.

^{1}H-NMR (DMSO-d$_6$): δ 12.25 (s, 1H), 9.28 (s, 1H), 9.02 (s, 1H), 7.53 (m, 3H), 7.39 (t, 2H, J = 7.6 Hz), 7.13 (d, 1H, J = 7.6 Hz), 7.11 (d, 1H, J = 8.4 Hz), 5.27 (m, 2H), 4.54 (d, 1H, J = 17.2 Hz), 4.38 (d, 2H, J = 17.6 Hz), 4.22 (m, 2H), 4.00 (dd, 1H, J = 17.2 Hz and J = 5.2 Hz), 3.86 (s, 1H), 3.64 (d, 1H, J = 17.2 Hz), 2.81 (dd, 1H, J = 18 Hz and J = 7.2 Hz);

LC-MS: R$_t$ = 2.96 min; m/z: 522 [M+H]$^+$

EXAMPLE 15

5-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

To a solution of trifluoroacetic acid (0.5 ml) and dichloromethane (0.5 ml) was added 2-(*tert*-butoxyoxalyl-amino)-5-(7-(*tert*-butyl-dimethyl-silanyloxy)-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (11 mg, 0.014 mmol). The solution was stirred at room temperature for 16 hours. The reaction mixture was poured into ethyl ether (20 ml). The precipitate was filtered off and dried in vacuo, which afforded 7.0 mg (79 %) of the title compound as a solid trifluoroacetate.

^{1}H-NMR (DMSO-d$_6$): δ 12.39 (s, 1H), 9.95 (s, 1H), 9.75 (s, 2H), 7.42 (t, 1H, J = 8.0 Hz), 7.30 (s, 2H), 7.02 (d, 1H, J = 7.2 Hz), 6.96 (s, 2H), 6.85 (d, 1H, J = 7.2 Hz), 4.95-3.65 (m, 11H), 3.76 (s, 3H).

LC-MS: R$_t$ = 1.93 min, m/z: 553 [M+H]$^+$

76

EXAMPLE 16

5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

To a stirred solution of 2-amino-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (15 mg, 0.028 mmol) in tetrahydrofuran (1.0 ml) was added imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (27 mg, 0.11 mmol) in tetrahydrofuran (1.0 ml). The mixture was stirred at room temperature for 24 hours. The solvent was removed in vacuo. The residue was taken into ethyl acetate (20 ml). The solution was washed with 0.5 N hydrochloric acid solution (2 x 10 ml), saturated sodium bicarbonate (2 x 10 ml) and brine (10 ml), dried (MgSO₄) and filtered. The solvent was removed in vacuo. The residue was chromatographed using a gradient of 10-25 % ethyl acetate/hexane as eluent, which afforded 17 mg (93 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as a solid.

¹H-NMR (CDCl₃): δ 12.54 (s, 1H), 7.86 (m, 2H), 7.40 (m, 2H), 7.08 (d, 2H, J = 8.4 Hz), 6.72 (d, 2H, J = 8.4 Hz), 4.08 (dd, 1H, J = 13.6 Hz and J = 8.8 Hz), 3.94 (d, 1H, J = 16.8 Hz), 3.82 (d, 1H, J = 12.8 Hz), 3.78 (s, 3H), 3.92 (s, 3H), 3.70-3.56 (m, 3H), 3.53 (d, 1H, J = 12.8), 2.93 (dd, 1H, J = 16.8 Hz and J = 4.8 Hz), 2.75 (dd, 1H, J = 18.0 Hz and J = 5.6 Hz), 1.61 (s, 9H), 1.58 (s, 9H).

To a solution of trifluoroacetic acid (0.5 ml) and dichloromethane (0.5 ml) was added 2-(*tert*-butoxyoxalyl-amino)-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (15 mg, 0.023 mmol). The solution was stirred at room temperature for 40 hours. The reaction mixture was poured into ethyl ether (20 ml). The precipitate was filtered off and dried in vacuo, which afforded 13 mg (87 %) of the title compound as a solid trifluoroacetate.

¹H-NMR (DMSO-d₆): δ 12.38 (s, 1H), 7.89 (d, 4H, J = 11.2 Hz), 7.18 (s, 2H), 6.85 (s, 2H), 4.20-3.60 (m, 9H), 3.71 (s, 3H);

LC-MS: R$_t$ = 2.05 min, m/z: 550 [M+H]⁺

EXAMPLE 17

7-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-
thieno[2,3-c]pyridine-3-carboxylic acid

5

To a solution of 2-amino-7-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-
c]pyridine-3-carboxylic acid *tert*-butyl ester (80 mg, 0.20 mmol) and diisopropyl ethylamine
(35 µl, 0.40 mmol) in acetonitrile (10 ml) at room temperature was added a solution of 6-
bromomethyl-2-(*tert*-butyl-dimethyl-silanyloxy)-benzoic acid ethyl ester (69 mg, 0.20 mmol).

10   The solution was stirred for 12 hours at room temperature and the solvent was evaporated in
vacuo. The residue was dissolved in ethyl acetate (50 ml) and washed with water, 1 N hy-
drochloric acid, brine, dried (MgSO$_4$), filtered and the solvent evaporated in vacuo. The resi-
due was chromatographed on silica gel column eluted with 20 % ethyl acetate/hexane to
yield 42 mg (33 %) of 2-amino-7-(7-(*tert*-butyl-dimethyl-silanyloxy)-1-oxo-1,3-dihydro-

15   isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-
carboxylic acid *tert*-butyl ester as an oil.

^{1}H-NMR (CDCl$_3$): δ 7.64 (d, 1H, J = 8.8 Hz), 7.39 (t, 1H, J = 8.0 Hz), 7.10-6.80 (m,
5H), 6.09 (s, 2H), 5.0-4.2 (m, 4H), 3.80 (s, 3H), 3.66-2.92 (m, 3H), 1.55 (s, 9H), 1.04 (s, 9H),
0.22 (s, 6H).

20   To a stirred solution of 2-amino-7-(7-(*tert*-butyl-dimethyl-silanyloxy)-1-oxo-1,3-
dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-
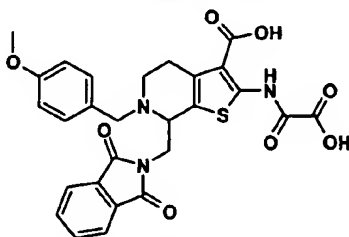carboxylic acid *tert*-butyl ester (40 mg, 0.060 mmol) in tetrahydrofuran (1 ml) was added imi-
dazol-1-yl-oxo-acetic acid *tert*-butyl ester (59 mg, 0.30 mmol) in tetrahydrofuran (1 ml). The
mixture was stirred at room temperature for 24 hours. The solvent was removed in vacuo.

25   The residue was dissolved in ethyl acetate (20 ml) and the solution was washed with 0.5 N
hydrochloric acid (2 x 20 ml), saturated sodium bicarbonate (2 x 20 ml), brine (20 ml), dried
(MgSO$_4$) and filtered. The solvent was removed in vacuo and the residue was chromatograp-
hed using a gradient of 10-20 % ethyl acetate/Hexane as eluent, which afforded 40 mg (83
%) of 2-(*tert*-butoxyoxalyl-amino)-7-(7-(*tert*-butyl-dimethyl-silanyloxy)-1-oxo-1,3-dihydro-

30   isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-
carboxylic acid *tert*-butyl ester as a solid.

^{1}H-NMR (CDCl$_3$): δ 12.52 (s, 1H), 7.37 (t, 1H, J = 8.0 Hz), 6.97 (d, 2H, J = 8.4 Hz), 6.94 (d, 1H, J = 8.0 Hz), 6.83 (d, 1H, J = 8.0 Hz), 6.54 (d, 1H, J = 8.4 Hz), 4.26 (d, 1H, J = 16.8 Hz), 3.93-3.84 (m, 2H), 3.77 (d, 1H, J = 16.8 Hz), 3.69 (s, 3H), 3.66-3.48 (m, 3H), 3.42-3.32 (m, 1H), 2.95 (dd, 1H, J = 14.4 Hz and J = 4.8 Hz), 2.92-2.82 (m, 1H), 2.73 (dd, 1H, J =

5   14.4 Hz and J = 4.8 Hz), 1.60 (s, 9H), 1.59 (s, 9H), 1.02 (s, 9H), 0.22 (d, 6H, J = 1.6 Hz).

To a solution of 2-(*tert*-butoxyoxalyl-amino)-7-(7-(*tert*-butyl-dimethyl-silanyloxy)-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (4.0 mg, 5.1 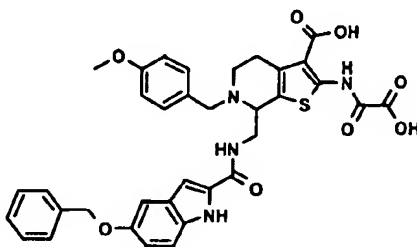   mol) in 10 % formic acid/methanol (1 ml) at room temperature under nitrogen was added 10 % Pd/C (4 mg). The mixture was

10   stirred for 1 hour. The Pd/C was filtered off and the filtrate was evaporated in vacuo to afford 2.8 mg (82 %) of 2-(*tert*-butoxyoxalyl-amino)-7-(7-(*tert*-butyl-dimethyl-silanyloxy)-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-5H-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as a solid.

^{1}H-NMR (CDCl$_3$): δ 12.45 (s, 1H), 8.05 (s, 1H), 7.39 (t, 1H, J = 8.0 Hz), 6.99 (d, 1H,

15   J = 8.0 Hz), 6.79 (d, 1H, J = 8.0 Hz), 4.50 (d, 1H, J = 17.2 Hz), 4.45 (d, 1H, J = 17.2 Hz), 4.24 (d, 1H, 8.4 Hz), 4.03 (dd, 1H, J = 16.0 Hz and J = 7.2 Hz), 3.78-3.68 (m, 2H), 3.38-3.28 (m, 1H), 3.21 (d, 1H, J = 18.8 Hz), 3.08-2.98 (m, 1H), 1.57 (s, 9H), 1.56 (s, 9H), 0.98 (s, 9H), 0.15 (d, 6H, J = 1 Hz).

To a solution of trifluoroacetic acid (0.5 ml) and dichloromethane (0.5 ml) was added

20   2-(*tert*-butoxyoxalyl-amino)-7-(7-(*tert*-butyl-dimethyl-silanyloxy)-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-5*H*-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (2.8 mg, 0.0042 mmol). The solution was stirred at room temperature for 16 hours. The solvent was removed in vacuo and the residue was washed with dichloromethane affording 1.8 mg (79 %) of the title compound as a solid trifluoroacetate.

25   ^{1}H-NMR (DMSO-d$_6$): δ 12.30 (s, 1H), 9.76 (s, 1H), 9.40 (s, 1H), 8.95 (s, 1H), 7.40 (t, 1H, J = 7.6 Hz), 7.00 (d, 1H, J = 7.6 Hz), 6.83 (d, 1H, J = 7.6 Hz), 4.92 (s, 1H), 4.54 (d, 1H, J = 18.4 Hz), 4.40 (d, 2H, J = 18.4 Hz), 4.08-4.00 (m, 1H), 3.91 (d, 1H, J = 15.2 Hz), 3.60 (s, 2H), 3.06 (s, 2H);

LC-MS: R$_t$: 1.41 min, m/z: 432 [M+H]$^+$

30

EXAMPLE 18

7-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-
4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

To a solution of trifluoroacetic acid (0.5 ml) and dichloromethane (0.5 ml) was added 2-(tert-
butoxyoxalyl-amino)-7-(7-(tert-butyl-dimethyl-silanyloxy)-1-oxo-1,3-dihydro-isoindol-2-
ylmethyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-
butyl ester (10 mg, 0.013 mmol). The solution was stirred at room temperature for 16 hours.
The solvent was removed in vacuo and the residue was washed with dichloromethane, which
afforded 6.8 mg (92 %) of the title compound as a solid trifluoroacetate.

^{1}H-NMR (DMSO-d$_6$): δ 12.35 (s, 1H), 9.90 (s, 1H), 9.70 (s, 2H), 7.41 (t, 1H, J = 8.0 Hz), 7.28
(s, 2H), 7.04 (d, 1H, J = 7.2 Hz), 6.92 (s, 2H), 6.83 (d, 1H, J = 7.2 Hz), 4.90-3.60 (m, 11H),
3.80 (s, 3H).

LC-MS: R$_t$ = 1.92 min, m/z: 552 [M+H]$^+$

EXAMPLE 19

7-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

To a stirred solution of 2-amino-7-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-
benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester (10 mg,
0.019 mmol) in tetrahydrofuran (1.0 ml) was added imidazol-1-yl-oxo-acetic acid tert-butyl
ester (18 mg, 0.092 mmol) in tetrahydrofuran (1.0 ml). The mixture was stirred at room tem-
perature for 24 hours. The solvent was removed in vacuo. The residue was dissolved in ethyl
acetate (20 ml) and washed with 0.5 N hydrochloric acid solution (2 x 10 ml), saturated so-

dium bicarbonate (2 x 10 ml), brine (10 ml), dried (MgSO₄), and filtered. The solvent was removed in vacuo and the residue was chromatographed using a gradient of 10-25 % ethyl acetate/hexane as eluent, which afforded 11 mg (89 %) of 2-(*tert*-butoxyoxalyl-amino-7-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-

5   c]pyridine-3-carboxylic acid *tert*-butyl ester as a solid.

^{1}H-NMR (CDCl₃): δ 12.54 (s, 1H), 7.76 (m, 4H), 6.82 (d, 2H, J = 11.6 Hz), 6.33 (d, 2H, J = 11.6 Hz), 4.02 (d, 1H, J = 14.4 Hz), 3.98 (d, 1H, J = 14.4 Hz), 3.62 (s, 3H), 3.62-3.54 (m, 2H), 3.48-3.34 (m, 2H), 3.02-2.70 (m, 3H), 1.60 (s, 9H), 1.59 (s, 9H).

To a solution of trifluoroacetic acid (0.5 ml) and dichloromethane (0.5 ml) was added

10   2-(*tert*-butoxyoxalyl-amino-7-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (10 mg, 0.015 mmol). The solution was stirred at room temperature for 16 hours. The solvent was removed in vacuo and the residue was washed with dichloromethane, which afforded 6.8 mg (80 %) of the title compound as a solid trifluoroacetate.

15   ^{1}H-NMR (DMSO-d₆): δ 12.38 (s, 1H), 7.86 (m, 4H), 6.82 (s, 2H), 6.30 (s, 2H), 4.00-2.86 (m, 9H), 3.58 (s, 3H);

LC-MS: R$_t$ = 2.02 min; m/z: 550 [M+H]$^+$

20   **EXAMPLE 20**

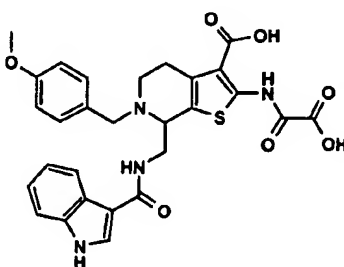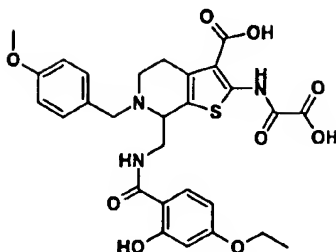**7-(((5-Benzyloxy-1*H*-indole-2-carbonyl)amino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid**

25   2-Amino-7-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester (0.50 g; 1.2 mmol) was dissolved in *N,N*-dimethylformamide (20 ml). 1-Hydroxy-7-azabenzotriazole (0.19 g; 1.3 mmol) and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (0.26 g; 1.3 mmol) and diisopropyl-ethylamine (0.23 ml; 1.3 mmol) were added and the mixture was stirred for 15 min. 5-Benzyloxyindole (0.36 g; 1.3

30   mmol) was dissolved in *N,N*-dimethylformamide (20 ml) and added. Diisopropylethylamine (0.23 ml; 1.3 mmol) was added and the mixture was stirred overnight. The solvent was re-

moved in vacuo, the residue dissolved in dichloromethane (30 ml) and the organic phase washed with an aqueous solution of sodium hydrogencarbonate (15 ml). The organic phase was dried (MgSO₄), filtered and the solvent removed in vacuo. The residue was chromatographed on silica using ethyl acetate/heptane (1:1) as eluent affording 569 mg of 2-amino-

5   7-(((5-benzyloxy-1H-indole-2-carbonyl)amino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester as an oil.

The title compound was prepared in a similar way as described in Example 1 using the two last steps.

10   MS: m/z: 669.4 [M+H]⁺

Calculated for $C_{35}H_{32}N_4O_8S$, $2/3xC_2HF_3O_2$, $4/3xH_2O$;

C, 56.77%; H, 4.63%; N, 7.29%. Found:

C, 56.43%; H, 4.57%; N, 7.13%.

15

EXAMPLE 21

7-(((6-Bromo-2-p-tolyl-quinoline-4-carbonyl)amino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)- 4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

20   The title compound was prepared in a similar way as in Example 19 using 6-bromo-2-p-tolyl-quinoline-4-carboxylic acid and 2-amino-7-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester as the starting material.
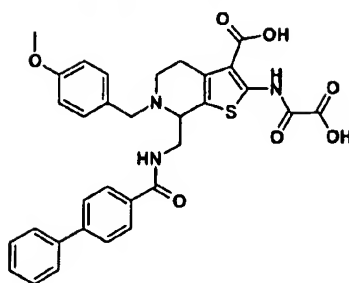
LC-MS: m/z: 745.2 [M+H]⁺

Calculated for $C_{36}H_{31}BrN_4O_7S$, $2xC_2HF_3O_2$;

25   C, 49.44%; H, 3.42%; N, 5.77%. Found:

C, 49.19%; H, 3.59%; N, 6.00%.

30

EXAMPLE 22

6-(4-Methoxy-benzyl)-7-(((5-methyl-2-phenyl-2H-[1,2,3]triazole-4-carbonyl)amino)methyl)-2-
(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

The title compound was prepared in a similar way as in Example 19 using 5-methyl-2-phenyl-
2H-[1,2,3]triazole-4-carboxylic acid and 2-amino-7-aminomethyl-6-(4-methoxy-benzyl)-
4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester as the starting mate-
rial.

LC-MS: m/z: 605.2 [M+H]$^+$

Calculated for $C_{29}H_{28}N_6O_7S$, $1.3xC_2HF_3O_2$, $1.7xH_2O$;

C, 48.14%; H, 3.94%; N, 10.94%. Found:

C, 48.35%; H, 4.19%; N, 10.68%.

EXAMPLE 23

7-(((1H-Indole-3-carbonyl)amino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

The title compound was prepared in a similar way as in Example 19 using 3-indole-carboxylic
acid and 2-amino-7-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-
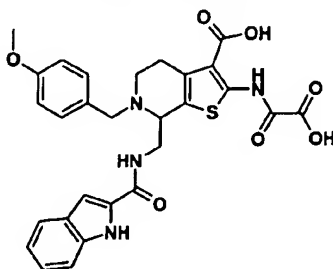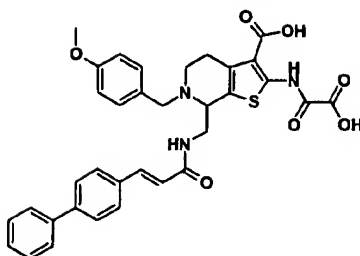c]pyridine-3-carboxylic acid tert-butyl ester as the starting material.

LC-MS: m/z: 563.2 [M+H]$^+$

Calculated for $C_{28}H_{26}N_4O_7S$, $5/3xC_2HF_3O_2$;

C, 49.63%; H, 3.82%; N, 7.35%. Found:

C, 50.00%; H, 3.71%; N, 7.44%.

EXAMPLE 24

5   7-((4-Ethoxy-2-hydroxy-benzoylamino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-
4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

The title compound was prepared in a similar way as in Example 19 using 4-ethoxy-2-
hydroxy-benzoic acid and 2-amino-7-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-
10   thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as the starting material.
LC-MS: m/z: 584 [M+H]$^+$
HPLC: (B6): 23.8 min.

EXAMPLE 25

15

7-((4-Benzoylamino-benzoylamino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

The title compound was prepared in a similar way as in Example 19 using 4-
20   benzoylaminobenzoic acid and 2-amino-7-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as the starting material.
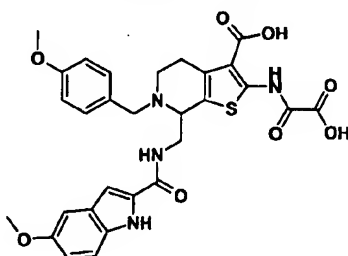LC-MS: m/z: 643.1 [M+H]$^+$
Calculated for $C_{33}H_{30}N_4O_8S$, $3xC_2HF_3O_2$;
C, 47.57%; H, 3.38%; N, 5.69%. Found:
25   C, 47.34%; H, 3.55%; N, 5.62%.

EXAMPLE 26

7-(((Biphenyl-4-carbonyl)amino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-
5 tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

The title compound was prepared in a similar way as in Example 19 using 4-phenylbenzoic
acid and 2-amino-7-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-
c]pyridine-3-carboxylic acid *tert*-butyl ester as the starting material.

10

LC-MS: m/z: 599.0 [M+H]$^+$
Calculated for $C_{32}H_{29}N_3O_7S$, $2xC_2HF_3O_2$, $1xH_2O$;
C, 51.13%; H, 3.93%; N, 4.97%. Found:
C, 52.02%; H, 4.02%; N, 5.16%.

15

EXAMPLE 27

7-(((1*H*-Indole-2-carbonyl)amino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

20

The title compound was prepared in a similar way as in Example 19 using indole-2-carboxylic
acid and 2-amino-7-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-
c]pyridine-3-carboxylic acid *tert*-butyl ester as the starting material.
LC-MS: m/z: 563.2 [M+H]$^+$
25 HPLC (B6) R_t = 23.07 min.

EXAMPLE 28

7-((3-Biphenyl-4-yl-acryloylamino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

5

The title compound was prepared in a similar way as in Example 19 using 3-biphenyl-4-yl-acrylic acid and 2-amino-7-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as the starting material.
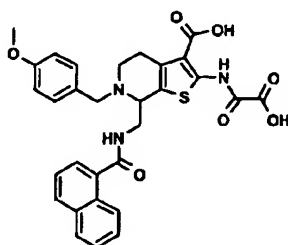
10 LC-MS: m/z: 626.2 [M+H]$^+$
HPLC (B6) R_t = 28.74 min.

Calculated for $C_{34}H_{31}N_3O_7S$, $2xC_2HF_3O_2$:
C, 53.46%; H, 3.90%; N, 4.92%. Found:
15 C, 53.89%; H, 4.23%; N, 5.08%.

EXAMPLE 29

6-(4-Methoxy-benzyl)-7-(((5-methoxy-1*H*-indole-2-carbonyl)amino)-methyl)-2-(oxalyl-amino)-
20 4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

The title compound was prepared in a similar way as in Example 19 using 5-methoxyindole-2-carboxylic acid and 2-amino-7-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as the starting material.
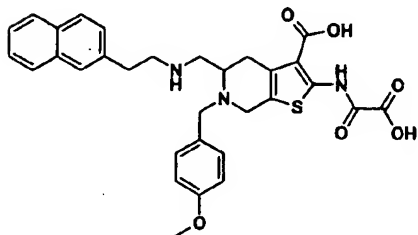25 LC-MS: m/z: 593.2 [M+H]$^+$
HPLC (B6) R_t = 21.81 min.

EXAMPLE 30

7-((4-Benzyl-benzoylamino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-
5   tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

The title compound was prepared in a similar way as in Example 19 using 4-benzylbenzoic
acid and 2-amino-7-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-
c]pyridine-3-carboxylic acid tert-butyl ester as the starting material.

10   LC-MS: m/z: 614.2 [M+H]$^+$

HPLC (B6) R$_t$ = 27.23 min.

Calculated for $C_{33}H_{31}N_3O_7S$, $1.5xC_2HF_3O_2$, $1xH_2O$;

C, 53.87%; H, 4.33%; N, 5.23%. Found:

C, 53.92%; H, 4.24%; N, 5.18%.

15

EXAMPLE 31

6-(4-Methoxy-benzyl)-7-(((naphthalene-1-carbonyl)amino)methyl)-2-(oxalyl-amino)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

20

The title compound was prepared in a similar way as in Example 19 using 1-
napthylcarboxylic acid and 2-amino-7-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-
thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester as the starting material.

25   LC-MS: m/z: 574.0 [M+H]$^+$

HPLC (B6) R$_t$ = 22.51 min.

Calculated for C₃₀H₂₇N₃O₇S, 2xC₂HF₃O₂;

C, 50.94%; H, 3.65%; N, 5.24%. Found:

C, 51.39%; H, 3.79%; N, 5.16%.

5

EXAMPLE 32

6-(4-Methoxy-benzyl)-5-((2-naphthalen-2-yl-ethylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

10

A solution of 2-naphthalen-2-yl-ethanol (1.02 g, 5.8 mmol), 2,2,6,6-tetramethyl-1-
piperidinyloxy (TEMPO) (9 mg, 0.058 mmol) and sodium bromide (0.65 g, 6.4 mmol) in a
mixture of toluene (18 mL), ethyl acetate (18 mL), and water (3mL) was cooled to 0 °C and
added dropwise over 1 hour a solution containing the following: sodium hypochlorite (17.2

15   mL, 0.37 M, 6.4 mmol) and sodium hydrogencarbonate (1.46 g, 17.4 mmol). The reaction
mixture was stirred at 0 °C for 10 min., and the phases separated. The aqueous layer was
extracted with ethyl acetate (150 mL). The combined organic phases were washed with a
solution of potassium iodone (0.2 g) in 10 % aqueous potassium hydrogensulfate (150 mL),
water (150 mL), brine (150 mL), dried (MgSO₄), filtered, and concentrated in vacuo to provide

20   980 mg of a 3:1 mixture of naphthalen-2-yl-acetaldehyde and 2-naphthalen-2-yl-ethanol.
¹H-NMR (CDCl₃): δ 9.81 (t, 1H, J = 1.5 Hz), 7.92-7.80 (m, 3H), 7.68 (bs, 1H), 7.55-7.42 (m,
3H), 3.87 (d, 2H, J = 1.5 Hz).

To a solution of 2-amino-5-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-
thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester (290 mg, 0.71 mmol) in 1,2-

25   dichloroethane (3 ml) was added the above mixture of 2-naphthyl-acetaldehyde (100 mg,
0.59 mmol), sodium triacetoxyborohydride (190 mg, 0.88 mmol) and the mixture was stirred
at room temperature under nitrogen for 2.5 hours. The crude reaction mixture was quenched
with saturated sodium bicarbonate (50 ml) and the solution extracted with ethyl acetate (100
ml). The organic phase was dried (MgSO₄), filtered, and concentrated in vacuo providing a

30   foam, which was taken directly to the next step. LC-MS showed that 2-amino-6-(4-methoxy-

88

benzyl)-5-((2-naphthalen-2-yl-ethylamino)-methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester was the major component.

LC-MS: m/z: 558.1 [M+H]$^+$, R$_f$ = 2.23 min.

To a solution of 2-amino-6-(4-methoxy-benzyl)-5-((2-naphthalen-2-yl-
5   ethylamino)methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester in tetrahydrofuran (3 ml) was added di-*tert*-butyl-dicarbonate (188 mg, 0.85 mmol) and *N,N*-dimethylformamide (18 mg, 0.14 mmol). The reaction was stirred at room temperature for 7 hours under nitrogen. The crude reaction mixture was diluted with dichloromethane (50 ml) and washed with water (50 ml) and brine (50 ml). The organic phase was dried (MgSO$_4$), fil-
10   tered, and concentrated in vacuo affording a foam, which was used without further purification in the next step.

LC-MS showed that 2-amino-5-((*tert*-butoxycarbonyl-(2-naphthalen-2-yl-ethyl)-amino)-methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester was the major component.

15   R$_f$= 2.74, m/z: 658.1 [M+H]$^+$, Calculated: 657.4.

To crude 2-amino-5-((*tert*-butoxycarbonyl-(2-naphthalen-2-yl-ethyl)-amino)-methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester was added dichloromethane (5 ml) and imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (400 mg, 1.78 mmol) and the reaction mixture stirred at room temperature for 12 hours. The crude
20   reaction mixture was added to dichloromethane (50 ml) and washed with water (50 ml) and brine (50 ml). The organic phase was dried (MgSO$_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography using a mixture of dichloromethane/ethyl acetate (10:1) as eluent, which afforded 20.3 mg (39 % over tree steps) of 2-(*tert*-butoxyoxalyl-amino)-5-((*tert*-butoxycarbonyl-(2-naphthalen-2-yl-ethyl)-amino)methyl)-6-(4-
25   methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as a foam.

^{1}H NMR (CDCl$_3$) δ 7.99-7.92 (m, 3H), 7.88 (s, 1H), 7.68-7.57 (m, 3H), 7.45 (d, 2H, J = 7.8 Hz), 6.99 (d, 2H, J = 8.1 Hz), 3.90-3.75 (m, 7H), 3.56-3.42 (m, 5H), 3.19-3.13 (m, 2H), 2.88-2.82 (m, 2H), 1.79 (s, 9H), 1.71 (s, 18H);
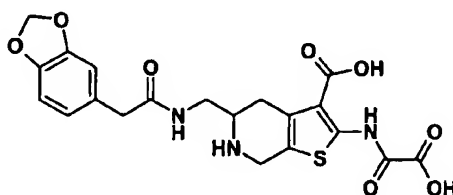30   LC-MS: m/z: 786.2 [M+H]$^+$, R$_f$ = 3.03 min.

To a solution of 2-(*tert*-butoxyoxalyl-amino)-5-((*tert*-butoxycarbonyl-(2-naphthalen-2-yl-ethyl)-amino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (20 mg, 0.03 mmol) in dry dichloromethane (200 µl) at 0 °C was added 50 % trifluoroacetic acid in dichloromethane (2.5 ml). The reaction was stirred for
35   14 hours at room temperature and then concentrated in vacuo. The resultant solid was re-

suspended in dichloromethane, filtered, and dried in vacuo to provide 13 mg (90 %) of the title compound as a solid.

^{1}H NMR (DMSO-d$_6$) δ 9.15 (s, 1H), 8.09-8.01 (m, 3H), 7.93 (s, 1H), 7.68-7.57 (m,
3H), 7.45 (d, 2H, J =7.8 Hz), 6.99 (d, 2H, J = 8.1 Hz), 4.18-4.12 (m, 2H), 3.90-3.75 (m, 7H),
5   3.56-3.42 (m, 3H), 3.19-3.13 (m, 2H), 2.88-2.82 (m, 2H);

LC-MS: m/z: 574.7 [M+H]$^+$, R$_f$ = 1.36 min.

EXAMPLE 33

10

5-((2-Benzo[1,3]dioxol-5-yl-acetylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-
thieno[2,3-c]pyridine-3-carboxylic acid

To a mixture of 2-amino-5-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-
15   c]pyridine-3-carboxylic acid tert-butyl ester (300 mg, 0.74 mmol), benzo[1,3]dioxol-5-yl-acetic
acid (134 mg, 0.74 mmol), 1-hydroxybenzotriazole hydrate (111 mg, 0.82 mmol), and N,N-
diisopropyl-ethylamine (258 μL, 1.48 mmol) in acetonitrile (5 ml) at room temperature was
added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (157 mg, 0.82 mmol).
The reaction mixture was stirred for 16 hours and the solvent evaporated in vacuo. The resi-
20   due was taken into ethylacetate (50 ml), washed with water, 1 N hydrochloric acid, saturated
sodium bicarbonate, brine, dried (MgSO$_4$), filtered and the solvent evaporated in vacuo. The
residue was subjected to flash chromatography using a gradient of 10-20% ethylaceta-
te/hexanes as eluent, which afforded 268 mg (64 %) of 2-amino-5-((2-benzo[1,3]dioxol-5-yl-
acetylamino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-
25   carboxylic acid tert-butyl ester as an oil.

^{1}H-NMR (CDCl$_3$) δ 6.95 (bs, 2H), 6.75-6.85 (m, 5H), 5.96 (bs, 2H), 5.95 (s, 2H),
3.81 (s, 3H), 3.75-3.30 (m, 5H), 3.53 (s, 2H), 3.18 (bs, 2H), 2.82 (d, 1H, J = 17 Hz), 2.52 (d,
1H, J = 17 Hz).

To a solution of 2-amino-5-((2-benzo[1,3]dioxol-5-yl-acetylamino)methyl)- 6-(4-
30   methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester
(133 mg, 0.235 mmol) in tetrahydrofuran (1 ml) was added imidazol-1-yl-oxo-acetic acid tert-
butyl ester (100 mg, 0.51 mmol). The mixture was stirred at room temperature for 24 hours.

The solvent was removed in vacuo. The residue was taken into ethyl acetate (50 ml) washed with saturated sodium bicarbonate, brine, dried (Na_2SO_4) and filtered. The solvent was removed in vacuo and the residue was chromatographed using a gradient of 10-20% ethyl acetate/dichloromethane, which afforded 130 mg (80 %) of 2-(*tert*-butoxyoxalyl-amino)-5-((2-

5   benzo[1,3]dioxol-5-yl-acetylamino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H-NMR (CDCl$_3$) δ 12.50 (s, 1H), 7.95-7.75 (m, 7H), 5.96 (s, 2H), 3.81 (s, 3H), 3.80-3.40 (m, 5H), 3.15 (bs, 2H), 2.90 (d, 1H, J = 17 Hz), 2.58 (d, 1H, J = 17 Hz), 1.61 (s, 9H), 1.60 (s, 9H).

10   A solution of 2-(*tert*-butoxyoxalyl-amino)-5-((2-benzo[1,3]dioxol-5-yl-acetylamino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (130 mg, 0.188 mmol) in tetrahydrofuran (2 ml) was passed through a Raney Ni bed (120 mg, 50% Raney Ni-water washed with methanol (6 ml) and tetrahydrofuran (6 ml) and dried before use). The Raney Ni bed was washed with tetrahydrofu-

15   ran (10 ml). The filtrate and washes were combined and the solvent evaporated in vacuo. The residue was dissolved in 10% formic acid/methanol (6 ml) and stirred with 10% Pd/C (120 mg) for 13 hours. Saturated sodium bicarbonate solution (60 ml) was added to the solution. The mixture was extracted with dichloromethane. The extracts were combined, dried (Na_2SO_4) and filtered. The solvent was removed in vacuo and the residue was washed with

20   50% hexane/diethyl ether to afford 62 mg (57 %) of 2-(*tert*-butoxyoxalyl-amino)-5-((2-benzo[1,3]dioxol-5-yl-acetylamino)methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as an oil.
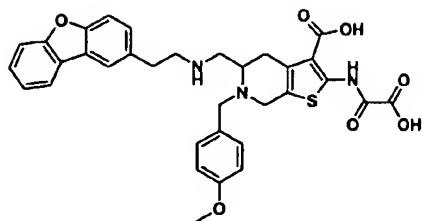
^{1}H-NMR (CDCl$_3$) δ 12.59 (s, 1H), 6.80-6.70 (m, 3H), 5.96 (s, 2H), 4.05 (q, 2H, J = 15 Hz), 3.85-3.60 (m, 2H), 3.25-3.00 (m, 4H), 2.58 (m, 1H), 1.61 (s, 9H), 1.59 (s, 9H);

25   LC-MS: R$_t$ = 1.75 min, m/z: 574 [M+H]$^+$.

A solution of 2-(*tert*-butoxyoxalyl-amino)-5-((2-benzo[1,3]dioxol-5-yl-acetylamino)methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (62 mg, 0.11 mmol) in 50% trifluoroacetic acid-dichloromethane (2 ml) was left in an open flask over the weekend and then the solvent was removed in vacuo. The residue was was-

30   hed with dichloromethane and the solid filtered off affording 39 mg (62 %) of the title compounds as a solid trifluoroacetate.

^{1}H-NMR (DMSO-d$_6$) δ 12.39 (s, 1H), 9.18 (bs, 1H), 9.10 (bs, 1H), 8.35 (s, 1H), 6.83 (d, 1H, J = 1.2 Hz), 6.82 (d, 1H, J = 8.4 Hz), 6.70 (dd, 1H, J = 8.4 Hz and J = 1.2 Hz), 5.96 (s, 2H), 4.38 (d, 1H, J = 14 Hz), 4.28 (m, 1H), 3.60-3.40 (m, 4H), 3.16 (d, 2H, J = 14 Hz), 2.80

35   (dd, 1H, J = 14 Hz and J = 11 Hz);

LC-MS: R$_t$ = 1.11 min, m/z: 462 [M+H]$^+$.

EXAMPLE 34

<u>5-((2-Dibenzofuran-2-yl-ethyl)amino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-</u>
<u>tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid</u>

To a solution of 2-dibenzofuran-2-yl-ethanol (200 mg, 0.94 mmol) and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (2 mg, 0.009 mmol) in dichloromethane (2 mL) was added an · aqueous solution of sodium bromide (97 mg in 1.3 mL of water for a 0.7M solution, 0.94mmol) and cooled to 0 °C. To this mixture was added dropwise over 30 min., a solution containing the following: sodium hypochlorite (1.4 mL, 0.74 M, 1.03 mmol) and sodium hydrogencarbonate (120 mg, 1.4 mmol) and water (1.4 mL). The reaction mixture was stirred at 0 °C for 0.5 hour and allowed to warm to room temperature. The organic phase and aqueous layer were separated and the aqueous layer extracted with dichloromethane (20 mL). The combined organic phases were washed with a solution of potassium iodone (0.2 g) in 10% aq. Potassium hydrogensulfate (20 mL), water (20 mL), brine (20 mL), dried (MgSO$_4$) filtered, and concentrated <u>in vacuo</u> to provide 198 mg of a 5:1 mixture of dibenzofuran-2-yl-acetaldehyde and 2-dibenzofuran-2-yl-ethanol as an oil. ^{1}H-NMR (CDCl$_3$): δ 9.80 (t, 1H, J = 1.5 Hz), 8.02 (d, 2H, J = 8.2 Hz), 7.71 (bs, 1H), 7.75-7.42 (m, 4H), 3.82 (d, 2H, J = 1.5 Hz).

To a solution of 2-amino-5-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester (340 mg, 0.85 mmol) in 1,2-dichloroethane (3 ml) was added the above mixture of dibenzofuran-2-yl-acetaldehyde (150 mg, 0.70 mmol), and sodium triacetoxyborohydride (225 mg, 1.07 mmol) and the mixture was stirred at room temperature under nitrogen for 2.5 hours. The crude reaction mixture was quenched with saturated sodium bicarbonate (50 ml) and the solution extracted with ethylacetate (100 ml). The organic phase dried (MgSO$_4$), filtered, and the solvent evaporated <u>in vacuo.</u> The crude residue was taken directly to the next step. LC-MS showed that 2-amino-5-((2-dibenzofuran-2-yl-ethylamino)methyl]-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester was the major component in the crude mixture: m/z: 598.1 [M+H]$^+$, R$_f$ = 2.40 min).

Crude 2-amino-5-((2-dibenzofuran-2-yl-ethylamino)methyl]-6-(4-methoxy-benzyl)-
4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester was diluted in tetra-
hydrofuran (3 ml) and di-*tert*-butyl dicarbonate (262 mg, 1.20 mmol) and 4-(*N,N*-
dimethylamino)pyridine (25 mg, 0.20 mmol) were added. The reaction was stirred at room

5   temperature for 7 hours under nitrogen. The crude reaction mixture was added to dichloro-
methane (50 ml) and washed with water (50 ml) and brine (50 ml). The organic phase was
dried (MgSO$_4$), filtered, and concentrated in vacuo. The residue was used directly in the next
step. LC-MS showed that 2-amino-5-((*tert*-butoxycarbonyl-(2-dibenzofuran-2-yl-ethyl)amino)-
methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-

10   butyl ester was the major component in the crude: R$_f$ = 2.76, m/z: 698.2 [M+H]$^+$.

To compound 2-amino-5-((*tert*-butoxycarbonyl-(2-dibenzofuran-2-yl-ethyl)amino)-
methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-
butyl ester was added dichloromethane (5ml) and imidazol-1-yl-oxo-acetic acid *tert*-butyl
ester (420 mg, 2.12 mmol). The reaction mixture was stirred at room temperature for 12

15   hours. The crude reaction mixture was added to dichloromethane (50 ml) and washed with
water (50 ml) and brine (50 ml). The organic phase was dried (MgSO$_4$), filtered, and con-
centrated in vacuo. The residue was subjected to flash chromatography using a mixture of
dichloromethane/ethyl acetate (10:1) as eluent, which afforded 35.2 mg (51 % over 3 steps)
of 2-(*tert*-butoxyoxalyl-amino)-5-((*tert*-butoxycarbonyl-(2-dibenzofuran-2-yl-

20   ethyl)amino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-
carboxylic acid *tert*-butyl ester as a foam.

^{1}H-NMR (CDCl$_3$) δ 7.95-7.90 (m, 3H), 7.84 (s, 1H), 7.68-7.57 (m, 3H), 7.45 (d, 2H, J
= 7.8 Hz), 6.95 (m, 3H), 3.90-3.75 (m, 7H), 3.56-3.42 (m, 5H), 3.19-3.13 (m, 2H), 2.88-2.82
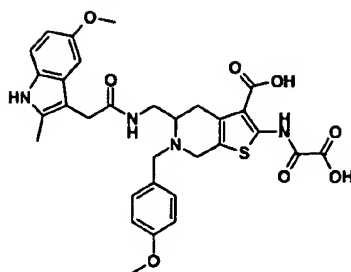(m, 2H), 1.79 (s, 9H), 1.71 (s, 18H);

25   LC-MS: R$_f$ = 3.03 min, m/z: 826.2 [M+H]$^+$.

To a solution of 2-(*tert*-butoxyoxalyl-amino)-5-((*tert*-butoxycarbonyl-(2-dibenzofuran-
2-yl-ethyl)amino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-
carboxylic acid *tert*-butyl ester (28 mg, 0.034 mmol) in dry dichloromethane (200 μL) at 0 °C
was added 50% trifluoroacetic acid in dichloromethane (2.5 ml). The reaction was stirred for

30   14 hours at room temperature and then concentrated in vacuo. The resultant solid was re-
suspended in dichloromethane, filtered, and dried in vacuo, which afforded 22 mg (90 %) of
the title compound as a solid trifluoroacetate.

^{1}H-NMR (DMSO-d$_6$) δ 9.15 (s, 1H), 8.11-8.21 (m, 3H), 7.93 (s, 1H), 7.68-7.57 (m,
3H), 7.45 (d, 2H, J = 7.8 Hz), 6.99 (d, 2H, J = 8.1 Hz), 4.18-4.12 (m, 2H), 3.90-3.75 (m, 7H),

35   3.56-3.42 (m, 3H), 3.19-3.13 (m, 2H), 2.88-2.82 (m, 2H);
LC-MS: R$_f$ = 3.03, m/z: 614.7 [M+H]$^+$.

<u>EXAMPLE 35</u>

<u>6-(4-Methoxy-benzyl)-5-((2-(5-methoxy-2-methyl-1*H*-indol-3-yl)-acetylamino)methyl)-2-
(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid</u>

5

To a solution of 2-amino-5-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-
c]pyridine-3-carboxylic acid *tert*-butyl ester (202 mg, 0.50 mmol), in *N,N*-dimethylformamide
(4 ml) was added 5-methoxy-2-methyl-3-indole acetic acid (170 mg, 0.74 mmol), 1-(3-
dimethylamino-propyl)-3-ethylcarbodiimide, hydrochloride (150 mg, 0.75 mmol), and 1-

10   hydroxybenzotriazole (105 mg, 0.74 mmol). The mixture was stirred at room temperature for
12 hours. The crude reaction mixture was diluted with dichloromethane (100 ml) and washed
with water (100 ml), brine (100 ml), dried (MgSO₄), filtered, and concentrated <u>in vacuo</u>, which
afforded 2-amino-6-(4-methoxy-benzyl)-5-((2-(5-methoxy-2-methyl-1*H*-indol-3-
yl)acetylamino)methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl

15   ester as an oil.

¹H-NMR (CDCl₃) δ 7.16 (d, 2H, *J* = 10.8 Hz), 6.99 (d, 1H, *J* = 2.5 Hz), 6.94 (m, 1H),
6.85 (dd, 1H, *J* = 8.4 Hz and *J* = 1.2 Hz), 6.78 (dd, 1H, *J* = 8.3 Hz and *J* = 1.2 Hz), 6.65 (m,
3H), 6.57 (m, 4H), 3.57 (t, 4H, *J* = 3.0 Hz), 3.53 (m, 6H), 3.59-3.29 (m, 5H), 3.12-2.92 (m,
4H), 2.39 (s, 3H), 1.6 (s, 9H);

20   LC-MS R$_t$= 2.19, m/z: 605 [M+H]⁺.

To a solution of 2-amino-6-(4-methoxy-benzyl)-5-((2-(5-methoxy-2-methyl-1*H*-indol-
3-yl)acetylamino)methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl
ester (96 mg, 0.5 mmol) in dichloromethane (5 ml) was added imidazol-1-yl-oxo-acetic acid
tert-butyl ester (583 mg, 3.0 mmol) and the reaction stirred at room temperature for 24 hours.

25   The mixture was then concentrated <u>in vacuo</u>. The residue was purified by flash column
chromatography (25% ethylacetate/dichloromethane) to give 53 mg (15 %) of 2-(*tert*-
butoxyoxalyl-amino)-6-(4-methoxy-benzyl)-5-((2-(5-methoxy-2-methyl-1*H*-indol-3-
yl)acetylamino)methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl
ester as an oil.

30   ¹H-NMR (CDCl₃) δ 7.16 (d, 2H, *J* = 10.8 Hz), 6.99 (d, 1H, *J* = 2.5 Hz), 6.94 (m, 1H),
6.85 (dd, 1H, *J* = 8.4 Hz and *J* = 1.2 Hz), 6.78 (dd, 1H, *J* = 8.3 Hz and *J* = 1.2 Hz), 6.65 (m,

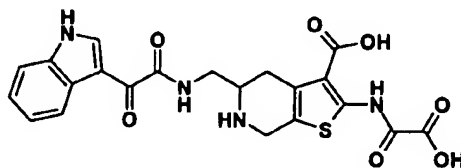3H), 6.56 (m, 3H), 3.57 (m, 3H), 3.53 (m, 6H), 3.59-3.29 (m, 5H), 3.12-2.92 (m, 4H), 2.39 (s, 3H), 1.6 (s, 18H);

LC-MS R_t = 2.36 min, m/z: 733 [M+H]$^+$.

2-(*tert*-Butoxyoxalyl-amino)-6-(4-methoxy-benzyl)-5-((2-(5-methoxy-2-methyl-1*H*-indol-3-yl)acetylamino)methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester was dissolved in 50% trifluoroacetic acid/dichloromethane (3 ml) and stirred at room temperature for 48 hours. The solvent was removed in vacuo and the residual trifluoroacetic acid was removed under reduced pressure to give 17 mg (49 %) of the title compound as a solid trifluoroacetate.

^{1}H-NMR (DMSO-d$_6$) δ 10.62 (s, 1H), 7.31 (s, 1H), 7.08 (d, 1H, J = 10.2 Hz), 6.93 (s, 2H), 6.58 (dd, 1H, J_1 = 5.25 Hz and J_2 = 2.8 Hz), 3.84-3.44 (m, 19H, partially obscured by solvent), 2.95 (s, 1H), 2.28 (s, 3H), 1.31 (s, 1H), 1.19 (s, 2H);

LC-MS R_t = 1.89 min, m/z: 621 [M+H]$^+$.

EXAMPLE 36

5-((2-(1*H*-Indol-3-yl)-2-oxo-acetylamino)methyl)-2-(Oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

To a solution of 2-amino-5-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (209 mg, 0.51 mmol) in dry *N,N*-dimethylformamide (4 ml) was added 3-indole-glyoxylic acid (141 mg, 0.74 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, hydrochloride (152 mg, 0.76 mmol), and 1-hydroxy-benzotriazole (100 mg, 0.74 mmol). The mixture was stirred at room temperature for 16 hours, diluted with dichloromethane (100 ml) and washed with water (100 ml), brine (100 ml), dried (MgSO$_4$), filtered, and concentrated in vacuo. The residue was subjected to flash chromatography using a mixture of ethyl acetate/hexanes (2:5) as eluent, which afforded 143 mg (40 %) of 2-amino-5-((2-(1*H*-indol-3-yl)-2-oxo-acetylamino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as an oil.

LC-MS R_t = 2.31 min, m/z: 574.9 [M+H]$^+$.

To a solution of 2-amino-5-((2-(1*H*-indol-3-yl)-2-oxo-acetylamino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (143 mg, 0.25 mmol) in dichloromethane (5 ml) was added imidazol-1-yl-oxo-acetic acid *tert*-

95

butyl ester (144 mg, 0.75 mmol) and the flask was purged with nitrogen. After 24 hours an additional portion of imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (169 mg, 0.86 mmol) was added and the reaction mixture allowed stirred for an additional 24 hours. The mixture was then concentrated in vacuo. The residue was purified by flash chromatography using a mix-

5   ture of ethyl acetate/hexanes (2:5) as eluent, which afforded 101 mg (58 %) of 2-(*tert*-butyoxyoxalyl-amino)-5-((2-(1*H*-indol-3-yl)-2-oxo-acetylamino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as a oil.

^{1}H-NMR (CDCl$_3$) δ 9.23 (s, 1H), 9.07 (d, 1H, J = 3.6 Hz), 8.50 (d, 1H, J = 7.6 Hz), 8.15 (d, 1H, J = 4.0 Hz), 7.47 (d, 2H, J = 7.2 Hz), 7.38-7.27 (m, 6H), 6.89 (d, 2H, J = 8.8 Hz), 3.87-

10   3.59 (m, 6H), 3.04 (dd, 2H, J = 23.6 Hz), 2.74 (dd, 2H, J = 22.4 Hz), 1.62 (s, 18H);
LC-MS R$_t$ = 2.49 min, m/z: 703 [M+H]$^+$.

2-(*tert*-Butyoxyoxalyl-amino)-5-((2-(1*H*-indol-3-yl)-2-oxo-acetylamino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (101 mg, 0.143 mmol) was dissolved in dry tetrahydrofuran (6 ml) and passed through a pi-

15   pette, plugged with cotton containing Raney 2800 Nickel (0.38 g). The pipette was flushed with dry tetrahydrofuran (6 ml) and the filtrate was concentrated in vacuo. Pd on carbon (10%, 102 mg, source: Avocado) and formic acid (10% in methanol, 5 ml) were added to the flask containing 2-(*tert*-Butyoxyoxalyl-amino)-5-((2-(1*H*-indol-3-yl)-2-oxo-acetylamino)methyl)-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl

20   ester. After stirring for 18 hours, the solution was filtered through a pad of celite and concentrated in vacuo. The residue was diluted in ethyl acetate, washed with saturated sodium bicarbonate (2 x 25 ml), brine (2 x 25 ml), dried (MgSO$_4$), filtered and concentrated in vacuo. The residue was subjected to flash chromatography using a mixtureof 10% methanol/dichloromethane as eluent, which afforded 2-(*tert*-butyoxyoxalyl-amino)-5-((2-(1*H*-indol-3-

25   yl)-2-oxo-acetylamino)methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester.

^{1}H-NMR (CDCl$_3$) δ 9.23 (s, 1H), 9.07 (d, 1H, J = 3.6 Hz), 8.50 (d, 1H, J = 7.6 Hz), 8.15 (d, 1H, J = 4.0 Hz), 7.27 (s, 2H), 7.09 (d, 1H, J = 8.8 Hz), 6.81 (d, 1H, J = 8.8 Hz), 3.79 (s, 1H), 2.29 (s, 1H), 1.62-1.57 (m, 18H), 0.08 (s, 5H);
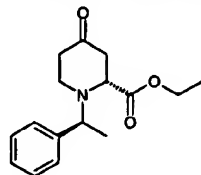
30   LC-MS: R$_t$ = 2.17 min, m/z: 583 [M+H]$^+$.

The above 2-(*tert*-butyoxyoxalyl-amino)-5-((2-(1*H*-indol-3-yl)-2-oxo-acetylamino)methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester was dissolved in 50% trifluoroacetic acid/dichloromethane (3 ml) and stirred at room temperature for 18 hours. The solvent was removed in vacuo and residual trifluoroacetic acid

35   was removed under reduced pressure affording 17.1 mg of the title compound as a solid trifluoroacetate.

^{1}H-NMR (DMSO-d$_6$) δ 12.28 (s, 2H), 9.26 (s, 1H), 9.13 (s, 1H), 8.83 (d, 1H, J = 2.8 Hz), 8.26 (d, 1H, J = 8.8 Hz), 7.55 (d, 1H, J = 4.8 Hz), 7.27 (d, 2H, J = 7.6 Hz), 4.42 (d, 1H, J = 15.2 Hz), 4.29 (d, 1H, J = 16.4 Hz), 3.76-3.22 (m, 4H, partially obscured by solvent), 2.91-2.834 (m, 1H), 1.23 (s, 1H); LC-MS: R$_t$ = 0.99 min, m/z 471.4 [M+H]$^+$.
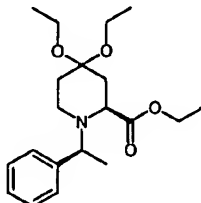
GENERAL CHIRAL SYNTHESIS

4-Oxo-1-((S)-1-phenyl-ethyl)-piperidine-(R)-2-carboxylic acid ethyl ester

Dichloromethane (1L) and mol sieves 3 Å (113 g) and amine (S)-(-)α-methylbenzylamin (71,7 ml) were mixed in a 2 l three-necked bottle cooled to –5 °C (using a ethanol/water/ice bath). A 50 % solution of ethylglyoxylate in toluene (117,6 ml) was added drop wise over 20 min., keeping the temperature between –5 °C and 0 °C The mixture was stirred for 0.5 hour before it was cooled to –30 °C. Trifluoroacetic acid (45,2 ml) was added over 3-4 minutes. Boron trifluoride diethyl ether (69,8 ml) was added drop wise over 5 min at –55 °C. The ice bath was removed and the mixture was allowed to warm up to –45 °C whereupon 2-(trimethylsilyloxy)-1,3-butadiene (100 ml) was added drop wise over 10 minutes. During the addition the mixture was cooled and the temperature kept below –20 °C. The above additions are all exothermic hence the cooling bath should have sufficient capacity to remove the heat generated during the rapid addition. The reaction mixture was stirred for 2 hours at –15 °C and 1 hour at 0 °C and then poured on ice/water and stirred for 15 minutes. Solid sodium hydrogen carbonate was added until pH 7-8. The mixture was stirred overnight at room temperature. The layers wee separated and the aqueous phase extracted with dichloromethane. The combined organic phases were filtered through a plug of silica eluting with dichloromethane. The relevant fractions were concentrated in vacuo. The residue was dissolved in hot heptane and cooled. This leaves a yellowish gummy material on the side of the flask and crystals starts forming. The heptane solution was heated again to dissolve crystals, leaving the gummy material on the side of the flask and the mixture was filtered hot. The heptane solution was cooled to room temperature and the precipitate was filtered off and dried in vacuo, which afforded 38 g of 4-oxo-1-((S)-1-phenyl-ethyl)-piperidine-(R)-2-carboxylic acid ethyl ester as a solid.
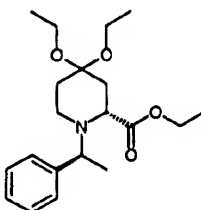
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The filtrate was put in a refrigerator and a second crop was formed which was less pure and needed recrystallization from heptane to yield another 7,5 g of 4-oxo-1-((S)-1-phenyl-ethyl)-piperidine-(R)-2-carboxylic acid ethyl ester.

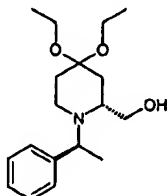5   **4,4-Diethoxy-1-((S)-1-phenyl-ethyl)-piperidine-(S)-2-carboxylic acid ethyl ester**

The mother liquor from the above crystallization was concentrated in vacuo. 5.0 g of the resulting material (18.16 mmol) was dissolved in ethanol (100 ml) and triethylorthoformate (26.9 g, 181.6 mmol) and para-toluensulphonic acid (6.9 g, 36.32 mmol) was added. The re-
10   action was stirred at room temperature for 16 hours before the mixture was poured on aqueous sodium hydrogen carbonate (200 ml) and extracted with ethyl acetate (4 x 75 ml). The combined extracts were concentrated in vacuo and purified by column chromatography (SiO$_2$, Flash 40, petrol ether-ethyl acetate 10:1). Collection of the first band (R$_f$ = 0.68) gave 1.14 g (18 %) of 4,4-diethoxy-1-((S)-1-phenyl-ethyl)-piperidine-(R)-2-carboxylic acid ethyl
15   ester and collection of the second band (R$_f$ = 0.4) gave 3.60 g (57 %) of the title compound.
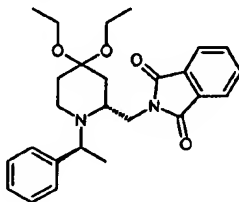
4,4-Diethoxy-1-((S)-1-phenyl-ethyl)-piperidine-(R)-2-carboxylic acid ethyl ester
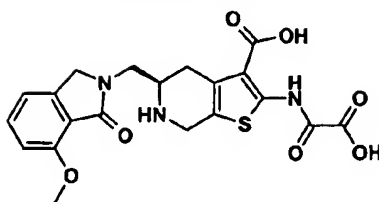

4-Oxo-1-((S)-1-phenyl-ethyl)-piperidine-(R)-2-carboxylic acid ethyl ester (11.0 g, 0.040 mmol)
20   was dissolved in a 1:1 mixture of triethyl orthoformate and ethanol (140 ml) and para-toluene-4-sulphonic acid (15.2 g, 80 mmol) was added and the reaction mixture was stirred for 16 hours. The reaction mixture was neutralized with sodium bicarbonate (to pH 7-8), and extracted with dichloromethane (3 x 100 ml), dried (MgSO$_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO$_2$, petrol ether/ethyl acetate
25   10:1), which afforded 12.0 g (86 %) of the title compound as an oil.

4,4-Diethoxy-1-((S)1-phenyl-ethyl)-(R)-2-hydroxymethyl-piperidine

To a solution of 4,4-diethoxy-1-((S)-1-phenyl-ethyl)-piperidine-(R)-2-carboxylic acid ethyl ester (36.0 g, 0.103 mol) in dry diethyl ether (150 ml) was added a suspension of lithium

5   aluminum hydride (5.88 g, 0.155 mol) in dry diethyl ether (300 ml) under an atmosphere of nitrogen at such a rate that the solution gently reflux. The reaction mixture was stirred over night before it was cooled to 0 °C and ethyl acetate (30 ml) was added drop wise to destroy excess lithium aluminum hydride. After stirring for another 0.5 hour, water (12 ml) was added drop wise. After stirring for 10-15 min the precipitate was filtered off through celite and the

10   filter cage was washed with plenty of diethyl ether. The filtrate was washed with brine (100 ml), dried (MgSO$_4$), filtered and the solvent evaporated in vacuo, which afforded 30 g (95 %) of the title compound as an oil.

4,4-Diethoxy-1-((S)-1-phenyl-ethyl)-(R)-2-phthalimidomethyl-piperidine

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A solution of 4,4-Diethoxy-1-((S)1-phenyl-ethyl)-(R)-2-hydroxymethyl-piperidine (65.35 g, 0.213 mmol), triphenylphosphine (61.3 g, 0.234 mol) and phthalimide (34.4 g, 0.234 mol) in tetrahydrofuran (700 ml) cooled to 0 °C was added diethyl azodicarboxylate over the course of 1.5 hour. The reaction mixture was stirred at 0 °C for another 2 hours before the solvent

20   was removed in vacuo. The residue was dissolved in hot heptane-toluene (3:2) (650 ml) be- fore it was cooled on an ice bath. The precipitate consisting of triphenyl phosphine oxide was filtered off and washed with heptane. The filtrate was concentrated in vacuo and the residue subjected to column chromatography using a mixture of toluene-ethyl acetate-heptane (3:1:3) as eluent. The solvent was evaporated in vacuo whereupon a viscous oil was obtai-

25   ned. Upon addition of light petrol ether the product crystallized to give 67.4 g (73 %) of the title compound as a solid.

EXAMPLE 37

5-(R)-(7-Methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-
thieno[2,3-c]pyridine-3-carboxylic acid

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A mixture of 4,4-diethoxy-1-((S)-1-phenyl-ethyl)-(R)-2-phthalimidomethyl-piperidine (5.25 g,
12.0 mmol) and hydrazine hydrate (2.92 ml, 60 mmol) was stirred overnight in ethanol (100
ml) at room temperature. The solvent was removed in vacuo and the solid residue was ex-
tracted with refluxing diethyl ether. The diethyl ether fractions were combined and evapora-

10   ted in vacuo, which afforded 3.94 g (94 %) of 4,4-diethoxy-1-((S)-1-phenyl-ethyl)-(R)-2-
aminomethyl-piperidine as an oil.

4,4-Diethoxy-1-((S)-1-phenyl-ethyl)-(R)-2-aminomethyl-piperidine (2.25 g, 7.37
mmol), and triethyl amine (1.49 g, 14.7 mmol) in acetonitrile (50 ml) was heated to 60 °C be-
fore 2-chlormethyl-6-methoxy-benzoic acid methyl ester (1.58 g, 7.37 mmol) in acetonitrile

15   (25 ml) was added over the course of 1.5 hour. After addition the reaction mixture was stirred
overnight at 60 °C. The solvent was removed in vacuo and the residue was dissolved in dich-
loromethane (50 ml) and washed with saturated sodium bicarbonate. After drying (MgSO₄),
filtration and evaporation of the solvent in vacuo the residue was subjected to flash column
chromatography (SiO₂, ethyl acetate-light petrol ether (1:1)) to give 2.3 g (69 %) of 2-(R)-(7-

20   methoxy-2,3-dihydro-isoindol-1-one-2-ylmethyl)-4,4-diethoxy-1-(1-(S)-phenyl-ethyl)-
piperidine.

2-(R)-(7-Methoxy-2,3-dihydro-isoindol-1-one-2-ylmethyl)-4,4-diethoxy-1(1-(S)-
phenyl-ethyl)-piperidine (2.0 g, 4.4 mmol) was dissolved in a ice cold mixture of trifluoroacetic
acid and water (10 ml, 9:1) and stirred or 0.5 hour on an ice bath. The reaction mixture was

25   poured on aqueous sodium carbonate (100 ml) and extracted with dichloromethane (2 x 50
ml). The organic phase was dried (MgSO₄), filtered and evaporated in vacuo, affording 1.67 g
(100 %) of 2-(R)-(7-methoxy-2,3-dihydro-isoindol-1-one-2-ylmethyl)-4-oxo-1(1-(S)-phenyl-
ethyl)-piperidine.

2-(R)-(7-Methoxy-2,3-dihydro-isoindol-1-one-2-ylmethyl)-4-oxo-1(1-(S)-phenyl-

30   ethyl)-piperidine (1.67 g, 4.41 mmol), sulphur (0.155 g, 4.85 mmol), tert-butylcyanoacetate
(0.684 g, 4.85 mmol), N-methylmorpholine (0.892 g, 8.82 mmol) and molecular sieves (4Å, 2
g) was heated to 50 °C in ethanol under an atmosphere of nitrogen for 16 hours. The reac-
tion mixture was filtered through a plug (1 cm) of SiO₂, the silica was washed with dichloro-

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methane-ethyl acetate and the solvent was removed in vacuo. The resulting residue was
subjected to column chromatography (Flash 40, SiO$_2$, toluene-ethyl acetate (3:1)), which
yielded 1.17 g (50 %) of 2-amino-5-(R)-(7-methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-
(1-(S)-phenyl-ethyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester

5   and 2-amino-7-(S)-(7-methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(1-(S)-phenyl-ethyl)-
4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester as a 3:1 mixture.

The above mixture of 5- and 7-regioisomers (1.17 g, 2.19 mmol) and imidazol-2-yl-
oxo-acetic acid tert-butyl ester (1.29 g, 7.57 mmol) and triethylamine (0.66 g, 6.57 mmol) was
stirred under an atmosphere of nitrogen in dichloromethane (25 ml) for 16 hours. The solvent

10 was removed in vacuo and the residue was subjected to column chromatography (SiO$_2$,
Flash 40, ethyl acetate-petrol ether (1:1)). Collection of relevant fractions gave 0.61 g (42 %)
of 2-(tert-butoxyoxalyl-amin)-5-(R)-(7-methoxy-1-oxo-1,3-dihydro-isoindo-2-ylmethyl)-6-(1-
(S)-phenyl-ethyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl
ester.

15   2-(tert-Butoxyoxalyl-amin)-5-(R)-(7-methoxy-1-oxo-1,3-dihydro-isoindo-2-ylmethyl)-
6-(1-(S)-phenyl-ethyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-
butyl ester (0.60 g, 0.91 mmol) was stirred for 16 hours in a mixture of methanol and formic
acid (10:1) (20 ml) in the presence of 10 % palladium on carbon (50 % water). The reaction
mixture was filtered through a plug of Celite and washed with methanol. The volatiles were

20 removed in vacuo and the residue was dissolved in dichloromethane (50 ml), washed with
semi saturated aqueous sodium carbonate (50 ml), dried (MgSO$_4$), filtered and the solvent
evaporated in vacuo. The residue was purified by column chromatography (SiO$_2$, Flash 40,
ethyl acetate-methanol (100:15)), which afforded 0.36 g (71 %) of 2-(tert-butoxyoxalyl-amin)-
5-(R)-(7-methoxy-1-oxo-1,3-dihydro-isoindo-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-
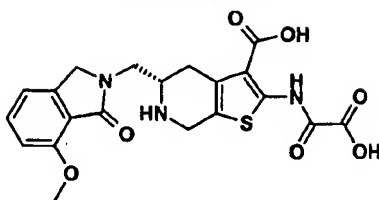
25 c]pyridine-3-carboxylic acid tert-butyl ester.

2-(tert-Butoxyoxalyl-amin)-5-(R)-(7-methoxy-1-oxo-1,3-dihydro-isoindo-2-ylmethyl)-
4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester (349 mg, 0.63 mmol)
was stirred for 16 hours in a mixture of trifluoroacetic acid and dichloromethane (1:1) (10 ml)
whereupon diethyl ether (20 ml) was added. The precipitate was filtered off and washed with

30 diethyl ether, which afforded 215 mg (61 %) of the title compound as a solid trifluoroacetate.
LC-MS: R$_t$ = 1.17 min, m/z: 446 [M+H]$^+$
Calculated for C$_{20}$H$_{19}$N$_3$O$_7$S, C$_2$HF$_3$O$_2$, 0.5xH$_2$O
C, 46.48%; H, 3.72%; N, 7.39%; Found:
C, 46.45%; H, 3.97%; N, 7.43%;

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EXAMPLE 38

5-(S)-(7-Methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

A solution of 4,4-diethoxy-1-((S)-1-phenyl-ethyl)-piperidine-(S)-2-carboxylic acid ethyl ester (35.98 g, 0.103 mol) in diethyl ether (150 ml) was added drop wise to a suspension of lithium aluminum hydride (5.88 g, 0.155 mol) in diethyl ether (300 ml) over the course of 1 hour. The reaction mixture was stirred at room temperature overnight before it was cooled on an ice bath and the reaction was quenched by dropwise addition of ethyl acetate (30 ml), followed by drop wise addition of water (12 ml) whereupon a gray precipitate was formed. The mixture was filtered through a plug of Celite and the filter cage was washed with plenty of diethyl ether. The filtrate was dried (MgSO₄) before it was filtered and the solvent removed in vacuo, which afforded 24.5 g (79 %) of 4,4-diethoxy-1-(1-(S)-phenyl-ethyl)-(S)-2-hydroxymethyl-piperidine as an oil.

A suspension of 4,4-diethoxy-1-(1-(S)-phenyl-ethyl)-(S)-2-hydroxymethyl-piperidine (20 g, 65 mmol), triphenylphosphine (18.76 g, 72 mmol) and phthalimide (10.52 g, 72 mmol) in tetrahydrofurane (200 ml) cooled to 0 °C was added diethyl azodicarboxylate (11.34 ml, 72 mmol) over the course of 1 hour. The reaction mixture was stirred at 0 °C for another 2 hours before the volatiles were removed in vacuo. The residue was dissolve in hot heptane-toluene (3:2) (100 ml) before it was cooled on an ice bath. The precipitate was filtered off and washed with heptane. The filtrate was concentrated in vacuo and the residue subjected to column chromatography using a mixture of toluene/ethyl acetate/heptane (3:1:3) as eluent. The solvent was evaporated in vacuo and the residue was crystallized by addition of light petrol ether (250 ml). The precipitate was filtered off, which afforded 24 g (85 %) of 4,4-diethoxy-1-(1-(S)-phenyl-ethyl)-2-(S)-phthalimidomethyl-piperidine as a solid.

4,4-Diethoxy-1-(1-(S)-phenyl-ethyl)-2-(S)-phthalimidomethyl-piperidine (4.0 g, 9.2 mmol) was dissolved in a mixture of trifluoroacetic acid and water (9:1) (100 ml) at 0 °C and stirred for 2 hours at this temperature. The mixture was basified with half saturated aqueous sodium carbonate, extracted with ethyl acetate and dried (MgSO₄) for 2 hours. The solvent was removed in vacuo and the residue was dried in a vacuum own at 40 °C for to days. This afforded 3.23 g (98 %) of 4-oxo-1-(1-(S)-phenyl-ethyl)-2-(S)-phthalimidomethyl-piperidine pure without further purification (98 %).
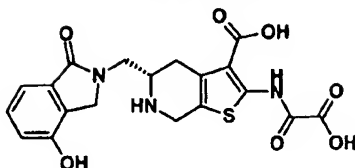
102

A mixture of 4-oxo-1-(1-(S)-phenyl-ethyl)-2-(S)-phthalimidomethyl-piperidine (17.28 g, 47.73 mmol), tert-butylcyanoacetat (7.41 g, 52.17 mmol), sulphur (1.71 g, 52.17 mmol) and morpholine (8.31 g, 95.46 mmol) in ethanol (150 ml) was heated under an atmosphere of nitrogen at 50 °C. The volatiles were removed in vacuo and the residue was subjected to
5   column chromatography on silica gel (heptane-ethyl acetate 5:1). The fractions consisting of a mixture of 5- and 7-isomer were collected and the solvent evaporated in vacuo. The residue was purified on a reverse phase (C$_{18}$) column using a Flash 40 system. The residue was applied in a minimum volume of acetonitrile and eluted with 40 % acetonitrile in water containing 0.1 % trifluoroacetic acid. When the 5-isomer was collected the eluent was changed
10   to 50 % acetonitrile in water with 0.1 % trifluoroacetic acid and the 7-isomer was collected. Yield of 2-amino-5-(S)-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(1-(S)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester was 7.96 g and yield of 2-amino-7-(R)-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(1-(S)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester was 3.72 g (47 % total).

15   2-Amino-5-(S)-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(1-(S)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester (7.96 g, 15.4 mmol) and hydrazine hydrate (3.85 g, 77.0 mmol) in ethanol (250 ml) was stirred for 16 hours at room temperature. The solvent was removed in vacuo and the solid residue was extracted with diethyl ether (3 x 200 ml). The fractions were combined and the solvent removed in
20   vacuo to give 5.9 g (100 %) of 2-amino-5-(S)-aminomethyl-6-(1-(S)-phenyl-ethyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester.

             2-Amino-5-(S)-aminomethyl-6-(1-(S)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester (0.55 g, 1.42 mmol) and triethylamine (396 l, 2.84 mmol) was heated in acetonitrile (15 ml) under an atmosphere of nitrogen to 60 °C
25   whereupon a solution of 2-chloromethyl-6-methoxy-benzoic acid methyl ester (0.32 g, 1.49 mmol) in acetonitrile (5 ml) was added dropwise over the course of 3 hours, keeping the reaction mixture at 60 °C. The reaction was allowed to cool to room temperature and was left for 16 hours before the solvent was evaporated in vacuo. The product was purified by column chromatography (SiO$_2$, Flash 40, ethyl acetate-petrol ether) to give 400 mg (53 %) of 2-
30   amino-5-(S)-(7-methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-((S)-1-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester as an oil.

The title compound was obtained as a trifluoroacetate in a similar way as described in example 32 using the last three steps.

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EXAMPLE 39

5-(S)-(4-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

3-Hydroxy-2-methylbenzoic acid (0.5 g, 3.2 mmol) was dissolved in HPLC grade methanol (5 ml) and cooled to 0 °C under nitrogen. Acetyl chloride (5 ml) was added dropwise. Once the addition was complete, the ice bath was removed and the reaction mixture allowed warming to room temperature over a period of 18 hours. The reaction was complete by tlc (R_f=0.5, 1:1 ethyl acetate/hexanes) and quenched with saturated sodium bicarbonate. The reaction mixture was concentrated, diluted with dichloromethane and water and the layers separated. The aqueous layer was extracted with dichloromethane (3x). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated in vacuo, which afforded 0.5 g (91 %) of 3-hydroxy-2-methylbenzoic acid methyl ester as a solid.

^{1}H-NMR ($CDCl_3$) δ 7.39 (dd, 1H, J = 8.1 Hz and J = 1.5 Hz), 7.09 (t, 1H, J = 8.1 Hz), 6.92 (dd, 1H, J = 8.1 Hz and J = 1.2 Hz), 5.11 (bs, 1H), 3.87 (s, 3H), 2.43 (s, 3H).

3-Hydroxy-2-methylbenzoic acid methyl ester (0.5 g, 3.01 mmol) in dichloromethane (15 ml) and N,N-diisopropylethylamine (1.57 ml, 9.03 mmol) was cooled to 0 °C under nitrogen. Chloromethyl methyl ether (0.46 ml, 6.02 mmol) was added dropwise and the reaction allowed warming to room temperature over a period of 18 hours. The reaction was judged to be 50 % complete by tlc (1:2 ethyl acetate/hexanes, I_2) and therefore, N,N-diisopropylethylamine (1.57 ml, 9.03 mmol) was added, the reaction mixture cooled to 0 °C and chloromethyl methyl ether (0.46 ml, 6.02 mmol) added once more. The reaction mixture was warmed to room temperature and stirred for 5 hours. The reaction was quenched with water and the layers separated. The aqueous layer was extracted once with dichloromethane and the organic layers combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by column chromatography (20 % ethyl acetate/hexanes) affording 0.44 g (69 %) of 3-methoxymethoxy-2-methyl-benzoic acid methyl ester as an oil.

^{1}H-NMR ($CDCl_3$) δ 7.46 (dd, 1H, J = 7.6 Hz and J = 1.2 Hz), 7.21 (dd, 1H, J = 8 Hz and J = 1.2 Hz), 7.18 (d, 1H, J = 8 Hz), 5.21 (s, 2H), 3.88 (s, 3H), 3.48 (s, 3H), 2.46 (s, 3H).

To a mixture of 3-methoxymethoxy-2-methyl-benzoic acid methyl ester (0.44 g, 2.09 mmol) in carbon tetrachloride (10 ml) was added N-bromosuccinimide (0.39 g, 2.19 mmol) and 1,1'-azo bis(cyclohexane-carbonitrile) (0.051 g, 0.21 mmol). The mixture was heated at

reflux for 3 hours, at which time the reaction was judged complete by tlc (1:4 ethyl aceta-
te/hexanes). The reaction mixture was cooled to room temperature and concentrated in va-
cuo to a solid. The solid was recrystallized from hexane leaving 0.44 g (82 %) of 2-
bromomethyl-3-methoxymethoxy-benzoic acid methyl ester as a solid.

5   ^{1}H-NMR (CDCl$_3$) δ 7.58 (dd, 1H, J = 6.8 Hz and J = 2.4 Hz), 7.33-7.29 (m, 2H), 5.30
(s, 2H), 5.07 (s, 2H), 3.94 (s, 3H), 3.52 (s, 3H).

To a stirred mixture of 2-amino-5-(S)-aminomethyl-6-(1-(S)-phenyl-ethyl)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester (0.24 g, 0.67 mmol) in ace-
tonitrile (30 ml) was added N,N-diisopropylethylamine (0.16 ml, 0.93 mmol) under nitrogen.

10   2-Bromo-methyl-3-methoxymethoxy-benzoic acid methyl ester (0.16 g, 0.55 mmol) dissolved
in acetonitrile, was added via syringe pump at a rate of 0.3 ml/hour. Once the addition was
complete, the reaction mixture was stirred at room temperature for 24 hours. Tlc analysis
(1:1 ethyl acetate/hexanes) indicated the reaction to be complete. The volatiles were remo-
ved in vacuo and the resultant oil dissolved in ethyl acetate/water. The layers were separated

15   and the aqueous layer extracted with ethyl acetate (3x). The organic layers were combined,
dried (MgSO$_4$), filtered and the solvebt evaporated in vacuo, which afforded 0.34 g (100 %)
of 2-amino-5-(S)-(4-methoxymethoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(1-(S)-phenyl-
ethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester, which was
used without further purification in the next step.

20   ^{1}H-NMR (CDCl$_3$) δ 7.51 (d, 1H, J = 6.8 Hz), 7.42 (t, 2H, J = 7.6 Hz), 7.23-7.17 (m,
5H), 5.93 (s, 2H), 5.25 (s, 2H), 4.23 (s, 2H), 4.12 (q, 1H, J = 7.2 Hz), 3.94 (m, 1H), 3.85 (q,
1H, J = 6.4 Hz), 3.66 (d, 1H, J = 16.4 Hz), 3.50 (s, 3H), 3.48-3.46 (m, 1H), 3.20 (dd, 1H, J =
14 Hz and J = 6 Hz), 2.94-2.87 (m, 1H), 2.60 (m, 1H), 1.49 (s, 9H), 1.36 (d, 3H, J = 6.4 Hz);
LC-MS: m/z: 564.1 [M+H]$^+$.

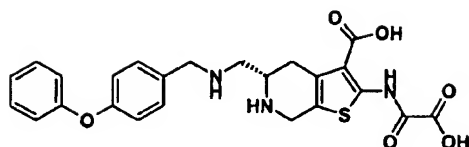25   To a solution of 2-amino-5-(S)-(4-methoxymethoxy-1-oxo-1,3-dihydro-isoindol-2-
ylmethyl)-6-(1-(S)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid
tert-butyl ester (0.34 g, 0.60 mmol) in dichloromethane (10 ml) was added imidazol-1-yl-oxo-
acetic acid tert-butyl ester (0.35 g, 1.8 mmol). The reaction mixture was stirred at room tem-
perature for 18 hours and the solvent concentrated in vacuo. The residue was dissolved in

30   ethyl acetate and washed with water (2 x 20 ml) and brine (2 x 25 ml). The organic layer was
dried (MgSO$_4$), filtered and the solvent evaporated in vacuo. The residue was subjected to
flash chromatography using a mixture of ethyl acetate/hexanes (1:1) as eluent. The obtained
residue was then subjected to chromatotron purification (1% methanol/ dichloromethane) and
later to another flash chromatography (20 % ethyl acetate/hexanes to 25 % ethyl aceta-

35   te/hexanes) to obtain 210 mg (50 %) of 2-(tert-butoxyoxalyl-amino)-5-(S)-(4-

methoxymethoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(1-(S)-phenyl-ethyl)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H-NMR (CDCl$_3$) δ 12.50 (s, 1H), 7.51 (dd, 1H, J = 6.8 Hz and J = 1.2 Hz), 7.42 (t,
2H, J = 8 Hz), 7.25-7.17 (m, 5H), 5.23 (s, 2H), 4.24 (q, 2H, J = 16.8 Hz), 4.08 (d, 1H, J = 16.8
5   Hz), 4.01 (dd, 1H, J = 14 Hz and J = 8.8 Hz), 3.89 (d, 1H, J = 17.6 Hz), 3.82 (q, 1H, J = 6.8
Hz), 3.56 (q, 1H, J = 6.4 Hz), 3.51 (s, 3H), 2.28 (dd, 1H, J = 14 Hz and J = 6.4), 2.98-2.92 (m,
1H), 2.69 (d, 1H, J = 17.2), 1.56 (s, 9H), 1.54 (s, 9H), 1.38 (d, 3H, J = 6.8 Hz);
LC-MS: m/z: 692.5 [M+H]$^+$.

To a solution of 2-(*tert*-butoxyoxalyl-amino)-5-(S)-(4-methoxymethoxy-1-oxo-1,3-
10   dihydro-isoindol-2-ylmethyl)-6-(1-(S)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-
carboxylic acid *tert*-butyl ester (0.16 g, 0.23 mmol) in formic acid (10 % in methanol, 5 ml to-
tal) was added 10% palladium on carbon (85 mg, source: Avacado) and the reaction mixture
allowed to stir at room temperature. After 6 hours, tlc (1:1 ethyl acetate/hexanes) analysis
indicated reaction complete. The reaction mixture was filtered through a pad of celite and
15   concentrated in vacuo. The crude product was purified via flash chromatography (gradient:
3% isopropyl alcohol/dichloromethane to 5 % isopropyl alcohol/dichloromethane (in 1% in-
crements of isopropyl alcohol)) to provide 0.11 g (82 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(S)-
(4-methoxymethoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-
c]pyridine-3-carboxylic acid *tert*-butyl ester as an oil.

20   ^{1}H-NMR (CDCl$_3$) δ 12.50 (bs, 1H), 7.48 (dd, 1H, J = 7.6 Hz and J = 0.8 Hz), 7.38 (t,
1H, J = 8 Hz), 7.22 (dd, 1H, J = 8 Hz and J = 0.8 Hz), 5.24 (s, 2H), 4.50 (q, 2H, J = 17.3 Hz),
4.02-3.90 (m, 2H), 3.74 (ddd, 2H, J = 34 Hz, J = 13.6 Hz and J = 5.6 Hz), 3.49 (s, 3H), 3.24
(m, 1H), 2.97 (ddd, 1H, J = 20 Hz, J = 4.4 Hz and J = 2.8 Hz), 2.50 (m, 1H), 1.59 (s, 9H),
1.51 (s, 9H);
25   LC-MS: m/z: 587.8 [M+H]$^+$.

2-(*tert*-Butoxyoxalyl-amino)-5-(S)-(4-methoxymethoxy-1-oxo-1,3-dihydro-isoindol-2-
ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (0.11 g,
0.18 mmol) was dissolved in neat trifluoroacetic acid (4 ml) and stirred at room temperature
for 48 hours. The reaction mixture was concentrated in vacuo and the resultant solid washed
30   with dichloromethane several times affording 100 mg (83 %) of the title compound as a solid
trifluoroaceatet.

^{1}H-NMR (DMSO-d$_6$) δ 12.29 (bs, 1H), 10.13 (s, 1H), 9.29 (bs, 1H), 9.10 (bs, 1H),
7.32 (t, 1H, J = 7.6 Hz), 7.17 (d, 1H, J = 7.2 Hz), 7.01 (d, 1H, J = 8 Hz), 4.52 (d, 1H, J = 17.2
Hz), 4.40-4.22 (m, 3H), 4.05 (dd, 1H, J = 14.4 Hz and J = 9.6 Hz), 3.90 (bs, 1H), 3.69 (dm,
35   1H), 3.22 (dm, 1H), 2.80 (dm, 1H);
LC-MS: m/z: 432.2 [M+H]$^+$.

EXAMPLE 40

2-(S)-(Oxalyl-amino)-5-((4-phenoxy-benzylamino)methyl)-4,5,6,7-tetrahydro-thieno[2,3-
c]pyridine-3-carboxylic acid

A solution of 2-amino-5-(S)-aminomethyl-6-(1-(S)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-
c]pyridine-3-carboxylic acid *tert*-butyl ester (500 mg, 1.29 mmol) and 4-
phenoxybenzaldehyde (256 mg, 1.29 mmol) was heated to 50 °C in ethanol (50 ml) for 1
hour in the presence of molecular sieves (4 A, 5 ml). The reaction mixture was cooled on an
ice bath before sodium borohydride (98 mg, 2.59 mmol) was added in three portions over 45
min. The cooling bath was removed and the reaction mixture was allowed to reach room
temperature. The mixture was filtered through a plug of Celite and the filter cage was washed
with dichloromethane (3 x 25 ml). The solvent was removed in vacuo and the residue was
redissolved in ethyl acetate (50 ml), washed with sodium bicarbonate (50 ml) and dried
(MgSO₄). The solvent was removed in vacuo before the residue was redissolved in aceto-
nitrile (20 ml). Triethylamine (130 mg, 1.29 mmol), di-*tert*-butyl dicarbonate (282 mg, 1.29
mmol) and 4-(N,N-dimethyl-amino)pyridine (5 mg, cat.) was added and the reaction mixture
was stirred for 16 hours at room temperature. The volatiles were removed in vacuo and ethyl
acetate (50 ml) was added and the solution was washed with saturated sodium bicarbonate
(50 ml) and dried (MgSO₄). The crude product was purified by column chromatography (SiO₂,
petroleum ether-ethyl acetate (9:1)) to give 325 mg (38% overall) of 2-amino-5-(S)-((4-
phenoxy-benzylamino)methyl)-6-(1-(S)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-
3-carboxylic acid *tert*-butyl ester.

The title compound was obtained as a trifluoroacetate in a similar way as described
in example 32 using the last three steps.

Oxalation: Standard procedure (16 hours, 82 %)

Hydrogenolysis: standard procedure (Pd/C, 10% Pd, methanol-formic acid, 16 hours, ((10:1))
(82% yield)

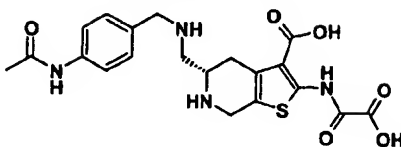TFA cleavage: Standard procedure. Yield 150 mg (87%).

LC-MS m/z: 482 [M+H]⁺, R$_t$ = 1.87 min

Calculated for C$_{24}$H$_{23}$N$_3$O$_6$S, 2x(C$_2$HF$_3$O$_2$)

C, 47.40%; H, 3.55%; N, 5.92%; Found:

C, 47.47%; H, 3.87%; N, 5.88%;

EXAMPLE 41

5-(S)-((4-Acetylamino-benzylamino)-methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid
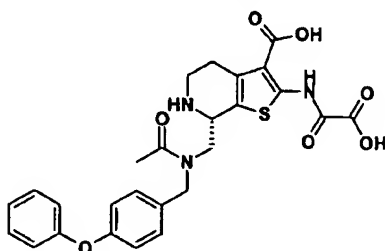
The title compound was prepared as a trifluoroacetate in a similar way as described in Example 35 using 2-amino-5-(S)-aminomethyl-6-(1-(S)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester and N-(4-formyl-phenyl)acetamide as the starting material.

Calculated for $C_{20}H_{22}N_4O_6S$, $1.5xC_2HF_3O_2$, $1.5xH_2O$

C, 43.78%; H, 3.99%; N, 8.88%; Found:

C, 44.20%; H, 4.43%; N, 8.75%;

EXAMPLE 42

7-(S)-((Acetyl-(4-phenoxy-benzyl)amino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

A solution of 2-amino-7-(S)-aminomethyl-6-(1-(S)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic aicd tert-butyl ester (500 mg, 1.29 mmol) and 4-phenoxybenzaldehyde (256 mg, 1.29 mmol) was heated to 50 °C in ethanol (50 ml) for 1 hour in the presence of molecular sieves (4 A, 5 ml). The reaction mixture was cooled on an ice bath before sodium borohydride (98 mg, 2.59 mmol) was added in three portions over 45

min. The cooling bath was removed and the reaction mixture was allowed to reach room
temperature. The mixture was filtered through a plug of Celite and the filter cage was washed
with dichloromethane (3 x 25 ml). The solvent was removed in vacuo and the residue was
redissolved in ethyl acetate (50 ml), washed with sodium bicarbonate (50 ml) and dried

5   (MgSO₄). The solvent was removed in vacuo before the product was dissolved in dichloro-
methane (10 ml). The solution was cooled on an ice bath before di-isopropyl-ethyl amine
(101 mg, 1.29 mmol) was added followed by drop wise addition of acetyl chloride (101 mg,
1.29 mmol) in dichloromethane (1 ml). The reaction mixture was stirred 1 hour at 0 °C and
the solution was washed with sodium bicarbonate (10 ml) and dried (MgSO₄). The crude

10   product was purified by flash column chromatography (SiO₂, ethyl acetate-petrol ether 1:3) to
give 320 mg (41%) of 7-(S)-((acetyl-(4-phenoxy-benzyl)amino)methyl)-2-amino-6-(1-(S)-
phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

        The title compound was obtained as a trifluoroacetate in a similar way as described
in example 32 using the last three steps.

15   Oxalation: Standard procedure (Yield 69%)
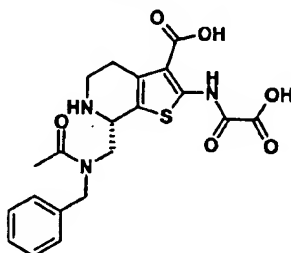Hydrogenolysis and trifluoroacetic acid cleavage in one step, Standard procedure (Overall
yield 6%)

LC-MS m/z = 524 [M+H]⁺, R$_t$ = 2.58 min

20   Calculated for C$_{26}$H$_{25}$N$_3$O$_7$S, C$_2$HF$_3$O$_2$, 0.5xH$_2$O
C, 52.01%; H, 4.21%; N, 6.50%; Found:
C, 51.82%; H, 4.34%; N, 6.36%.

25   EXAMPLE 43

7-(S)-((Acetyl-benzyl-amino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-
3-carboxylic acid

A solution of 2-amino-7-(S)-aminomethyl-6-(1-(S)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-

30   c]pyridine-3-carboxylic aicd tert-butyl ester (400 mg, 1.03 mmol) and benzaldehyde (105 mg,
1.03 mmol) was heated to 50 °C in ethanol (20 ml) for 1 hour in the presence of molecular

sieves (4 A, 7 ml). The reaction mixture was cooled on an ice bath before sodium borohydri-
de (78 mg, 2.06 mmol) was added in three portions over 45 min. The cooling bath was remo-
ved and the reaction mixture was allowed to reach room temperature. The mixture was filte-
red through a plug of Celite and the filter cage was washed with dichloromethane (3 x 25 ml).

5 The solvent was removed in vacuo and the residue was redissolved in ethyl acetate (50 ml),
washed with sodium bicarbonate (50 ml) and dried (MgSO₄). The solvent was removed in
vacuo before the product was dissolved in dichloromethane (20 ml). The solution was cooled
on an ice bath before di-isopropyl-ethyl amine (267 mg, 2.06 mmol) was added followed by
drop wise addition of acetyl chloride (81 mg, 1.03 mmol) in dichloromethane (1 ml). The reac-

10 tion mixture was stirred 1 hour at 0 °C before sodium bicarbonate (20 ml) was added. The
mixture was extracted with dichloromethane (2 x 10 ml) and the combined organic fractions
were dried (MgSO₄). The crude product was purified by flash column chromatography (petrol
ether/ethyl acetate (3:1)), which afforded 250 mg (46 %) of 7-(S)-((acetyl-benzyl-
amino)methyl)-2-amino-6-(1-(S)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-

15 carboxylic acid *tert*-butyl ester.

The title compound was obtained as a trifluoroacetate in a similar way as described
in example 32 using the last three steps.

Oxalation: Standard procedure (54%)

20 Hydrogenolysis: Standard procedure (methanol-formic acid (10:1)) Yield 38 mg (26%)
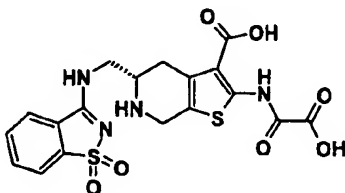Trifluoroacetic acid cleavage: Standard procedure 33 mg (80%)

LC-MS m/z: 432 [M+H]⁺, R$_t$ = 1.52 min
Calculated for C$_{20}$H$_{21}$N$_3$O$_6$S x 1.5xC$_2$HF$_3$O$_2$, 2xH$_2$O

25 C, 43.26%; H, 4.18%; N, 6.58%; Found:
C, 43.19%; H, 3.86%; N, 6.46%.

EXAMPLE 44

30 5-(S)-((1,1-Dioxo-1H-benzo[d]isothiazol-3-ylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

110

To a solution of (S)-2-amino-5-aminomethyl-6-(1-(S)-phenyl-ethyl)-4,5,6,7-tetrahydro-
thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester (1.0 g, 2.58 mmol) in dichloromethane
(10 ml) at 0 °C was added N,N-diisopropylethylamine (0.54 ml, 5.16 mmol). A solution of 3-
chloro-benzo[d]isothiazole 1,1-dioxide (0.52 g, 2.58 mmol) in dichloromethane (10 ml) was
5   then added dropwise and stirred for 30 min. The solution was warmed to room temperature
and washed with water and dried (MgSO₄). The solvent was then removed in vacuo. The re-
sidue was taken into dichloromethane (15 ml) and imidazol-1-yl-oxo-acetic acid tert-butyl
ester (1.0 g, 5.16 mmol) was added. The solution was stirred for 2 hours. The solvent was
removed in vacuo. The residue was taken into ethyl acetate (100 ml). The solution was was-
10   hed with 0.5 N hydrochloric acid solution, saturated sodium bicarbonate and brine, dried
(MgSO₄) and filtered. The solvent was removed in vacuo. The residue was chromatographed
using a mixture of 0-5% ethyl acetate/dichloromethane as eluent, which afforded 0.6 g (34
%) of 2-(tert-butoxyoxalyl-amino)-5-(S)-((1,1-dioxo-1H-benzo[d] isothiazol-3-ylamino)methyl)-
6-(1-(S)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl
15   ester as an oil

    ¹H-NMR (CDCl₃) δ 12.50 (s, 1H), 7.94-7.92 (m, 1H), 7.79-7.71 (m, 2H), 7.59-7.50
(m, 1H), 7.38-7.27 (m, 4H), 6.86 (d, 1H, J=4 Hz), 4.14 (d, 1H, J=12 Hz), 3.95 (d, 1H, J=17
Hz), 3.88 (q, 1H, J=6 Hz), 3.70-3.62 (m, 1H), 3.47 (t, 1H, J=13 Hz), 3.34-3.24 (m, 1H), 3.06
(dd, 1H, J=17, 6 Hz), 2.53 (d, 1H, J=17 Hz), 1.62 (s, 9H), 1.61 (s, 9H), 1.44 (d, 3H, J=7 Hz).

20   A solution of 2-(tert-butoxyoxalyl-amino)-5-(S)-((1,1-dioxo-1H-benzo[d] isothiazol-3-
ylamino)methyl)-6-(1-(S)-phenyl-ethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic
acid tert-butyl ester (252 mg, 0.37 mmol) in tetrahydrofuran (12 ml) was passed through Ra-
ney Ni (0.95 g, 50% Raney Ni-Water washed with methanol (6 ml) and tetrahydrofuran (10
ml) and dried before use). The solvent was removed in vacuo. The residue was dissolved in
25   acetic acid (7 ml) and hydrogenated with 10% Pd/C (250 mg) at 50 psi for 15 hours. The mix-
ture was filtered and the filtrate was added to saturated sodium bicarbonate solution. The
solution was then extracted with ethylacetate (3 x 100 ml). The extracts were combined and
dried (MgSO₄). The solvent was removed in vacuo. The residue was washed with diethyl
ether affording 156 mg (73 %) of 2-(tert-butoxyoxalyl-amino)-5-(S)-((1,1-dioxo-1H-benzo[d]
30   isothiazol-3-ylamino)-methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-
butyl ester as an oil.

    ¹H-NMR (CDCl₃) δ 12.59 (s, 1H), 7.94-7.90 (m, 1H), 7.70-7.66 (m, 3H), 7.51 (s, 1H),
4.11 (d, 1H, J=12 Hz), 4.08 (q, 2H, J=17 Hz), 3.40 (dd, 1H, J=12, 6 Hz), 3.26-3.18 (m, 1H),
3.18 (d, 1H, J=17 Hz), 2.55 (dd, 1H, J=12, 6 Hz), 1.62 (s, 18H).
35   LC-MS: Rₜ = 3.58 min, m/z: 577 [M+H]⁺.

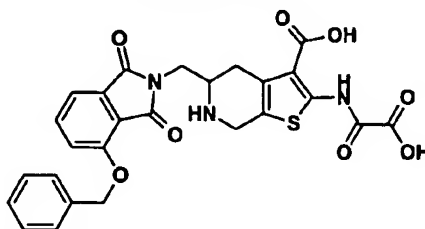A solution of 2-(*tert*-butoxyoxalyl-amino)-5-(*S*)-((1,1-dioxo-1*H*-benzo[d] isothiazol-3-ylamino)methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (149 mg, 0.26 mmol) in 50 % trifluoroacetic acid/dichloromethane (1 ml) was left in an open flask for 60 hours. The volatiles were removed in vacuo and the residue was washed with

5   dichloromethane to yield 80 mg (54 %) of the title compound as a solid trifluoroacetate.

^{1}H-NMR (DMSO-d_6) δ 12.29 (s, 1H), 9.80 (s, 1H), 9.51 (bs, 2H), 8.19 (d, 1H, J=5 Hz), 8.02-8.00 (m, 1H), 7.89-7.84 (m, 2H), 4.46 (d, 1H, J=16 Hz), 4.30 (d, 1H, J=16 Hz), 3.96-3.80 (m, 3H), 3.30 (d, 1H, J=17 Hz), 2.93 (dd, 1H, J=18, 10 Hz);

LC-MS: R_t = 0.68 min, m/z: 465 [M+H]$^+$.

10   **EXAMPLE 45**

5-(4-Benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

15   The title compound was prepared in a similar way as described in Example 5 as a trifluoroacetate.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.31 (s, 1H), 9.25 (bs, 2H), 7.80 (t, 1H, J = 8 Hz), 7.59-7.32 (m, 7H), 5.37 (s, 2H), 4.42-4.21 (m, 2H), 3.95-3.70 (m, 3H), 3.4-3.2 (obscured by water, 1H), 2.83-2.75 (m, 1H)

20   *LC-MS*: R_t = 2.16 min, m/z: 536.1 [M+H]$^+$

<div style="text-align:center">**EXAMPLE 46**</div>

25   5-(6-Methoxy-4-methoxycarbonyl-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

To a solution of 2-amino-5-aminomethyl-6-(4-methoxy-benzyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (57.4 mg, 0.142 mmol) and diisopropyl ethylamine (49 µl, 0.28 mmol) in acetonitrile (20 ml) at room temperature was added 2-bromomethyl-5-methoxy-isophthalic acid dimethyl ester (3.00 g, 7.45 mmol). The solution was stirred for 16

5   hours and the solvent evaporated in vacuo. The residue was taken into ethyl acetate (50 ml) and washed with water (2 x 20 ml), 1 N hydrochloric acid (20 ml), brine, dried (MgSO₄), filtered and the solvent evaporated in vacuo. The residue was chromatographed on silica gel column using a mixture of ethyl acetate/hexane (1:1) as eluent, which afforded 62 mg (71 %) of 2-amino-6-(4-methoxy-benzyl)-5-(6-methoxy-4-methoxycarbonyl-1-oxo-1,3-dihydro-isoindol-

10   2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as a solid.

^{1}H-NMR δ (CDCl₃): δ 7.75 (d, 1H, J = 2.4 Hz), 7.55 (d, 1H, J = 2.4 Hz), 7.11 (bs, 2H), 6.74 (d, 2H, J = 8.0 Hz), 5.97 (s, 2H), 4.71 (d, 1H, J = 18.4 Hz), 4.62 (d, 1H, J = 18.4 Hz), 4.09 (m, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.80 (m, 1H), 3.76 (s, 3H), 3.66-3.40 (m, 5H),

15   2.80 (d, 1H, J = 17.2 Hz), 2.64 (d, 1H, J = 17.2 Hz), 1.52 (s, 9H).

To a stirred solution of 2-amino-6-(4-methoxy-benzyl)-5-(6-methoxy-4-methoxycarbonyl-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (60 mg, 0.10 mmol) in tetrahydrofuran (1.0 ml) was added imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (60 mg, 0.30 mmol) in tetrahydrofu-

20   ran (1.0 ml). The mixture was stirred at room temperature for 24 hours. The solvent was removed in vacuo. The residue was taken into ethyl acetate (20 ml) and washed with 0.5 N hydrochloric acid (2 x 10 ml), saturated sodium bicarbonate (2 x 10 ml) and brine (10 ml), dried (MgSO₄) and filtered. The solvent was removed in vacuo and residue was chromatographed using a gradient ethyl acetate/hexane (10-25 %) as eluent, which afforded 40 mg (58 %) of

25   2-(*tert*-butoxyoxalyl-amino)-6-(4-methoxy-benzyl)-5-(6-methoxy-4-methoxycarbonyl-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as a solid.

^{1}H-NMR δ (CDCl₃): δ 12.54 (s, 1H), 7.75 (d, 1H, J = 2.4 Hz), 7.55 (d, 1H, J = 2.4 Hz), 7.10 (d, 2H, J = 8.0 Hz), 6.74 (d, 2H, J = 8.0 Hz), 4.74 (d, 1H, J = 18.4 Hz), 4.62 (d, 1H,

30   J = 18.4 Hz), 4.05-3.90 (m, 2H), 3.94 (s, 3H), 3.92 (s, 3H), 3.82-3.48 (m, 5H), 3.77 (s, 3H), 2.95 (dd, 1H, J = 17.2 Hz and J = 5.2 Hz), 2.67 (dd, 1H, J = 17.2 Hz and J = 5.2 Hz), 1.61 (s, 9H), 1.58 (s, 9H).

To a solution of 2-(*tert*-butoxyoxalyl-amino)-6-(4-methoxy-benzyl)-5-(6-methoxy-4-methoxycarbonyl-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (38 mg, 0.055 mmol) in 10 % formic

35   acid/methanol (1.0 ml) at room temperature under nitrogen was added 10 % Pd/C (38 mg).

The mixture was stirred for 16 hours and the Pd/C was filtered off and the filtrate evaporated in vacuo. The residue was taken into dichloromethane (1.0 ml) poured into hexane. The precipitate was filtered off, affording 28 mg (82 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(6-methoxy-4-methoxycarbonyl-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-
5 c]pyridine-3-carboxylic acid *tert*-butyl ester as a solid.

^{1}H-NMR δ (CDCl$_3$): δ 12.45 (s, 1H), 10.90 (s, 1H), 10.69 (s, H), 7.73 (s, 1H), 7.42 (s, 1H), 4.85 (bs, 2H), 4.65 (bs, 1H), 4.42 (bs, 2H), 3.99 (bs, 2H), 3.96 (s, 3H), 3.89 (s, 3H), 3.35 (bs, 1Hz), 3.21 (bs, 1H), 1.62 (s, 9H), 1.56 (s, 9H).

To a solution of trifluoroacetic acid (0.5 ml) and dichloromethane (0.5 ml) was added
10 2-(*tert*-butoxyoxalyl-amino)-5-(6-methoxy-4-methoxycarbonyl-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (14 mg, 0.023 mmol). The solution was stirred at room temperature for 40 hours. The reaction mixture was poured into diethyl ether (20 ml). The precipitate was filtered off, which afforded 10 mg (75 %) of the title compound as a solid trifluoroacetate.

15 ^{1}H-NMR δ (DMSO-d$_6$): δ 12.28 (s, 1H), 9.32 (s, 1H), 9.10 (s, 1H), 7.65 (d, 1H, J = 2.4 Hz), 7.50 (d, 1H, J = 2.4 Hz), 4.82 (d, 1H, J = 17.2 Hz), 4.65 (d, 1H, J = 17.6 Hz), 4.40 (d, 1H, J = 17.6 Hz), 4.30 (m, 1H), 4.10 (dd, 1H, J = 17.2 Hz and J = 5.2 Hz), 3.95 (s, 1H), 3.89 (s, 6H), 3.85 (d, 1H, J = 17.2 Hz), 2.81 (dd, 1H, J = 18 Hz and J = 7.2 Hz).
LC-MS: R$_t$ = 1.30 min; m/z: 504 [M+H]$^+$

20

EXAMPLE 47

2-(Oxalyl-amino)-5-(1,1,3-trioxo-1,3-dihydro-1*H*-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-
25 5*H*-thieno[2,3-c]pyridine-3-carboxylic acid
and
2-(Oxalyl-amino)-7-(1,1,3-trioxo-1,3-dihydro-1*H*-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-
5*H*-thieno[2,3-c]pyridine-3-carboxylic acid

30 To a solution of 2-aminomethyl-4-(2-spiro[1,3]dioxolane)-piperidine (193 mg, 1.12 mmol) and diisopropyl ethylamine (0.46 ml, 2.55 mmol) in acetonitrile (10 ml) cooled to 0 °C was added

114

2-chlorosulfonyl-benzoic acid methyl ester (278 mg. 1.18 mmol). The solution was stirred at 25 °C for 24 hours. Solvent was removed in vacuo and the residue was chromatographed using a mixture of ethyl acetate/hexane (1:3) as eluent, which afforded 199 mg (51 %) of 2-(4-(2-spiro[1,3]dioxolane)piperidin-2-ylmethyl)-1,1-dioxo-1,2-dihydro-1H-benzo[d]isothiazol-3-
5   one as a solid.

^{1}H-NMR (CDCl$_3$): δ 7.99-7.96 (m, 1H), 7.66-7.53 (m, 3H), 5.01 (s, 1H), 4.73 (dm, 1H, J = 14.4 Hz), 4.06-3.93 (m, 6H), 3.25 (dd, 1H, J = 12.6 Hz), 3.06 (td, 1H, J = 13.5 Hz and J = 3.6 Hz), 1.93 (dd, 1H, J = 14.1 Hz and J = 5.7 Hz), 1.87 (dd, 1H, J = 14.1 Hz and J = 3.0 Hz), 1.76 (dd, 1H, J = 13.5 Hz and J = 5.1 Hz).
10 LC-MS: R$_t$ = 1.78; m/z: 339 [M+H]$^+$.

2-(4-(2-Spiro[1,3]dioxolane)piperidin-2-ylmethyl)-1,1-dioxo-1,2-dihydro-1H-benzo[d]isothiazol-3-one (199 mg, 0.588 mmol) was dissolved in 2 M hydrochloric acid (12 ml) and the solution was heated to 50 °C for 24 hours. The volatiles were removed in vacuo and the residue (341 mg) was treated without further purification with saturated sodium car-
15 bonate (12 ml), dichloromethane (8 ml) and di-t-butyl dicarbonate (1.64 g, 7.5 mmol). The mixture was stirred at 35 °C for 3 days and extracted with dichloromethane (30 ml). The organic solution was washed with saturated sodium bicarbonate, brine, dried (MgSO$_4$), filtered and the solvent evaporated in vacuo. The residue was chromatographed on silica gel column using a mixture of ethyl acetate/hexane (1:3) as eluent, which afforded 115 mg (50 %) of 4-
20 oxo-2-(1,1,3-trioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl)-piperidine-1-carboxylic acid tert-butyl ester as an oil.

^{1}H-NMR (CDCl$_3$): δ 8.06 (dd, 1H, J = 6.0, 1.8 Hz), 7.95-7.80 (m, 3H), 5.02 (bs, 1H), 4.35 (bs, 1H), 3.91(dd, 1H, J = 15.0 Hz and J = 8.4 Hz), 3.78 (dd, 1H, J = 14.7 Hz and J = 5.7 Hz), 3.53 (t, 1H, J = 10.8 Hz), 2.74 (dd, 1H, J = 15.0 Hz and J = 7.5 Hz), 2.60-2.38 (m,
25 3H), 1.32 (s, 9H).

To a solution of 4-oxo-2-(1,1,3-trioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl)-piperidine-1-carboxylic acid tert-butyl ester (115 mg, 0.292 mmol) in absolute ethanol (5 ml) was added t-butyl cyanoacetate (57 l, 0.41 mmol), sulfur (13 mg, 0.41 mmol) and morpholine (55 μl, 0.63 mmol). The solution was stirred at 50 °C for 14 hours. The solvent was
30 evaporated in vacuo and the residue was chromatographed on silica gel column using a mixture of ethyl acetate/hexane (1:4) as eluent, which afforded 100 mg (62 %) of 2-amino-5-(1,1,3-trioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-tert-butyl ester and 2-amino-7-(1,1,3-trioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-
35 tert-butyl ester as a mixture.

¹H-NMR (CDCl₃): δ 8.10-8.00 (m, 1H), 7.98-7.77 (m, 2.8H), 7.66-7.58 (m, 0.2H),

6.11 (s, 0.4H), 6.06 (s, 0.6H), 5.59 (m, 0.2H), 5.39 (t, 0.3H, J = 5.7 Hz) 5.23 (bs, 0.3H), 5.04

(bs, 0.4H), 4.77 (d, 0.4H, J = 14.4 Hz), 4.60 (d, 0.4H, J = 14.4 Hz), 4.45-4.18 (m, 1H), 4.02-

3.82 (m, 1.5H), 3.64 (dd, 0.5H, J = 14.7 Hz and J = 5.2 Hz), 3.30-2.60 (m, 2H), 1.54 (s, 7H),

5   1.53 (s, 2H), 1.26 (s, 7H), 1.21 (s, 2H).

To a stirred solution of the above 2-amino-5-(1,1,3-trioxo-1,3-dihydro-1H-
benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-
tert-butyl ester and 2-amino-7-(1,1,3-trioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl)-
4,7-dihydro-5H-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-tert-butyl ester mixture (100 mg,

10   0.18 mmol) in acetonitrile (7 ml) was added imidazol-1-yl-oxo-acetic acid tert-butyl ester (290

mg, 1.46 mmol) in acetonitrile (1 ml). The mixture was stirred at room temperature for 16

hours. The solvent was removed in vacuo and the residue was taken into ethyl acetate. The

solution was washed with 0.5 N hydrochloric acid solution, saturated sodium bicarbonate,

brine, dried MgSO₄) and filtered. The solvent was removed in vacuo and the residue was

15   chromatographed on silicagel using a mixture of ethyl acetate/hexane (1:4) as eluent, which

provided 98 mg (80 %) of a mixture of 2-(tert-butoxyoxalyl-amino)-5-(1,1,3-trioxo-1,3-dihydro-
1H-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyridine-3,6-dicarboxylic acid

di-tert-butyl ester and 2-(tert-butoxyoxalyl-amino)-7-(1,1,3-trioxo-1,3-dihydro-1H-
benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-

20   tert-butyl ester as a solid.

¹H-NMR (CDCl₃): δ 12.60 (s, 0.3H), 12.54 (s, 0.7H), 8.12-8.06 (m, 1H), 7.98-7.80

(m, 2.8H), 7.66-7.58 (m, 0.2H), 5.83 (bs, 0.1H), 5.61 (t, 0.2H), 5.40-4.54 (m, 0.9H), 4.53-4.40

(m, 0.8H), 4.02-3.70 (m, 1.42H), 3.66 (dd, 0.58H, J = 14.7 Hz and J = 5.2 Hz), 3.30-2.99 (m,

3H), 1.68 (s, 6H), 1.62 (s, 6H), 1.60 (s, 6H), 1.31 (s, 4.5H), 1.25 (s, 4.5H);
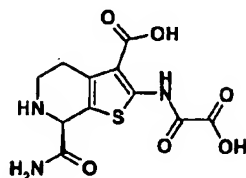
25   LC-MS: R₁ = 4.45; m/z: 678 [M+H]⁺.

To a solution of trifluoroacetic acid (4 ml) and dichloromethane (2 ml) was added the

mixture of 2-(tert-butoxyoxalyl-amino)-5-(1,1,3-trioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-
ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-tert-butyl ester and 2-
(tert-butoxyoxalyl-amino)-7-(1,1,3-trioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl)-4,7-

30   dihydro-5H-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-tert-butyl ester (78 mg, 0.12 mmol).

The solution was stirred at room temperature for 24 hours. The solvent was then evaporated

in vacuo, which afforded 50 mg (72 %) of the title compounds as a mixture of trifluoroaceta-

tes.

¹H-NMR (DMSO-d₆): δ 12.32 (s, 1H), 9.75-9.20 (m, 2H), 8.40 (t, 1H, J = 6.0 Hz),

35   8.22-8.02 (m, 3H), 5.03 (bs, 0.5H), 4.52 (d, 1H), 4.38-4.10 (m, 2H), 3.88 (bs, 0.5H), 3.70-3.64

(m, 0.5H), 3.44-3.34 (m, 0.5H), 3.20-2.90 (m, 2H).

LC-MS: R$_t$ = 1.28 min, m/z: 466 [M+H]$^+$

<div align="center">

EXAMPLE 48

</div>

5

7-(R)-Carbamoyl-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

To a solution of 2-(S)-4-oxo-piperidine-1,2-dicarboxylic acid 1-*tert* butyl ester (18.4 g,
75.6 mmol) and triethylamine (12.65 mL, 90.79 mmol) in tetrahydrofuran (50 mL) cooled to −

10   20°C was added isobutylchloro-formate (11.81 mL, 90.79 mmol) and the mixture was stirred
for 10 min at −20°C before a 25 % solution of ammonia in water (100 mL) was added. The
temperature was kept at -20°C for 30 min before the cooling bath was removed and the reac-
tion mixture was allowed to reach room temperature and stirring was continued for another
hour. The reaction mixture was extracted with ethyl acetate (6 x 50 mL) and the combined

15   organic phases were dried (MgSO$_4$). The solvent was removed in vacuo and the residue was
purified by column chromatography (SiO$_2$, Flash 40, ethyl acetate) to give 8.51 g (46 %) of 2-
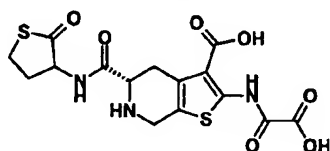(S)-carbamoyl-4-oxo-piperidine-1-carboxylic acid 1-*tert*-butyl ester.

A solution of 2-(S)-carbamoyl-4-oxo-piperidine-1-carboxylic acid 1-*tert* butyl ester
(3.51 g, 14.48 mmol), *tert*-butyl cyanoacetate (2.04 g, 14.48 mmol), sulphur (0.464 g, 14.48

20   mmol) and diisopropyl ethylamine (2.5 mL, 14.48 mmol) in methanol (20 mL) was heated 16
hours at 40°C under N$_2$. The volatiles were removed in vacuo and the residue was purified
using column chromatography (SiO$_2$, Flash 40, petroleum ether/ethyl acetate 3:1) to give
1.33 g (23%) of a mixture 2-amino-5-(S)-carbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyridine-3,6-
di-carboxylic acid di-*tert*-butyl ester and 2-amino-7-(R)-carbamoyl-4,7-dihydro-5H-thieno[2,3-

25   c]pyridine-3,6-di-carboxylic acid di-*tert*-butyl ester isomers.

0.5 g (1.25 mmol) of the above mixture was dissolved dichloromethane (10 mL) and
imidazole-1-yl-oxo-acetic acid *tert*-butyl ester (0.74 g, 3.77 mmol) and triethylamine (525 µL,
3.77 mmol) was added. The reaction mixture was stirred for 16 hours at room temperature
before the volatiles were removed in vacuo. The residue was purified by column chroma-

30   tography (SiO$_2$, Flash 40, petroleum ether/ethyl acetate (4:1)) too give 75 mg (11%) of 2-
(*tert*-butoxyoxalyl-amino)-7-(R)-carbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyridine-3,6-
dicarboxylic acid di-*tert*-butyl ester.

This was dissolved in a mixture of trifluoacetic acid/dichloromethane (1:1) (10 mL) and stirred for 16 hours at room temperature before the solvent was removed in vacuo. The residue was recrystallized from methanol to give 24 mg (39 %) of the title compound.

5   LC-MS; R_t = 1.56 min, m/z: 314 [M+H]⁺

Calculated for $C_{11}H_{11}N_3O_6S$, $0.25xC_2HF_3O_2$, $0.75xH_2O$

C, 38.88 %; H, 3.62 %; N, 11.83 %; Found:

C, 38.92 %; H, 3.92 %; N, 11.81 %.

10

EXAMPLE 49

2-(Oxalyl-amino)-5-(S)-(2-oxo-tetrahydro-thiophen-3-ylcarbamoyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

15   A solution of 2-amino-4,7-dihydro-5H-thieno[2,3-c]pyridine-3,5-(S),6-tri-carboxylic acid 3,6-di-tert-butyl ester (0.30 g, 0.75 mmol) and triethylamine (0.21 mL, 1.51 mmol) in tetrahydrofuran (10 mL) was cooled to -20°C before isobutyl chloroformate (103 µL, 0.75 mmol) was added. The reaction mixture was stirred 15 min at -20°C before homocystein hydrochloride (116 mg, 0.75 mmol) was added. The cooling bath was removed and the reaction mixture was left for

20   16 hours at room temperature. The solvent was removed in vacuo and the residue was subjected to column chromatography (SiO₂, Flash 40, heptane/ethyl acetate 2:1) to give 212 mg (56%) of 2-amino-5-(S)-(2-oxo-tetrahydro-thiophen-3-ylcarbamoyl)-4,7-dihydro-5H-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-tert-butyl ester

A solution of 2-amino-5-(S)-(2-oxo-tetrahydro-thiophen-3-ylcarbamoyl)-4,7-dihydro-5H-

25   thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-tert-butyl ester (200 mg, 0.40 mmol), imidazole-1-yl-oxo-acetic acid tert-butyl ester (235 mg, 1.20 mmol) and triethylamine (168 µL, 1.20 mmol) in dichloromethane (10 mL) was stirred for 16 hours at room temperature before the solvent was removed in vacuo. The residue was purified by column chromatography (SiO₂, Flash 40, heptane/ethyl acetate 2:1) to give 250 mg (100%) of 2-(tert-butoxyoxalyl-amino)-5-

30   (S)-(2-oxo-tetrahydro-thiophen-3-ylcarbamoyl)-4,7-dihydro-5H-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-tert-butyl ester.

This was dissolved in a mixture of trifluoroacetic acid/dichloromethane (1:1) (3 mL) and stirred for 16 hours at room temperature before diethyl ether (6 mL) was added. The precipi-

tate was filtered off and washed with diethyl ether to give 172 mg (81%) of the title compound as a solid trifluoroacetate.
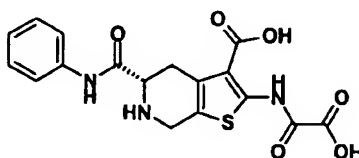
LC-MS; R_t = 0.41 min, m/z: 414 [M+H]$^+$

Calculated for $C_{15}H_{15}N_3O_7S_2$, 1.5x$C_2HF_3O_2$, H_2O;

5   C, 35.88 %; H, 3.10 %; N, 6.97 %; Found:

C, 35.91 %; H, 3.54 %; N, 6.97 %.

EXAMPLE 50

10   2-(Oxalyl-amino)-5-(S)-phenylcarbamoyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

A solution of 2-amino-4,5,6,7-tetrahydro-thieno[2,3-c]-pyridine-3,5-(S),6-tricarboxylic acid 3,5-di-tert-butyl ester (300 mg, 0.75 mmol) and triethylamine (210 μL, 1.51 mmol) in tetra-

15   hydrofuran (10 mL) was cooled to -20°C before isobutylchloroformate (103 mg, 0.75 mmol) was introduced. The reaction mixture was stirred for 20 min before aniline (70 mg, 0.75 mmol) was added. The cooling bath was removed and the reaction was left for 16 hours at room temperature before the solvent was removed in vacuo. The residue was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic phase was dried (MgSO$_4$)

20   and the solvent was removed in vacuo. The residue was dissolved in dichloromethane (10 mL) and imidazole-1-yl-oxo-acetic acid tert-butyl ester (443 mg, 2.26 mmol) and triethylamine (315 μL, 2.26 mmol) was added. The reaction mixture was stirred 16 hours at room temperature before the solvent was removed in vacuo. The residue was purified by column chromatography (SiO$_2$, Flash 40, heptane/ethyl acetate (3:1) to give 250 mg 2-(tert-butoxyoxalyl-

25   amino)-5-(S)-phenylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-tert-butyl ester.

2-(tert-Butoxyoxalyl-amino)-5-(S)-phenylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyridine-3,6-dicarboxylic acid di-tert-butyl ester was dissolved in a mixture of trifluoroacetic acid/dichloromethane (1:1) (3 mL) and stirred for 16 hours at room temperature before di-

30   ethyl ether (6 mL) was added. The precipitate was filtered off and washed with diethyl ether to give 155 mg (41%) of the title compound as a solid trifluoroacetate.
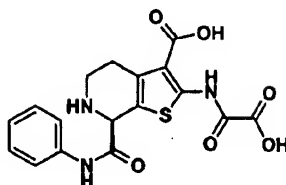
LC-MS; R_t = 0.86 min, m/z: 390 [M+H]$^+$

Calculated for $C_{17}H_{15}N_3O_6S$, 1.5x$C_2HF_3O_2$, H_2O;

C, 41.53 %; H, 3.22 %; N, 7.26 %; Found:

C, 41.77 %; H, 3.29 %; N, 7.28 %.

EXAMPLE 51

2-(Oxalyl-amino)-7-(R)-phenylcarbamoyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

To a solution of 2-(S)-4-oxo-piperidine-1,2-dicarboxylic acid 1-*tert* butyl ester (2.06 g, 8.47 mmol) and triethylamine (1.42 mL, 10.16 mmol) in tetrahydrofuran (20 mL) cooled to -20°C was added isobutylchloroformate (1.39 g, 10.16 mmol) and the mixture was stirred for 10 min at -20°C before aniline (946 mg, 10.16 mmol) was added. The cooling bath was removed and the reaction mixture was stirred for 16 hours at room temperature before the solvent was removed in vacuo. The residue was divided between water (50 mL) and ethyl acetate (50 mL). The organic phase was washed with saturated sodium chloride (25 mL) and dried (MgSO₄). After filtration and concentration in vacuo the residue was purified using column chromatography (SiO₂, Flash 40, petroleum ether/ethyl acetate 5:1) to give 1.3 g (48%) of 4- . oxo-2-(S)-phenyl-carbamoyl-piperidine-1-carboxylic acid *tert*-butyl ester.

A solution of 4-oxo-2-(S)-phenylcarbamoyl-piperidine-1-carboxylic acid *tert*-butyl ester (1.3 g, 4.08 mmol), *tert*-butylcyanoacetate (0.58 g, 4.08 mmol), sulphur (0.133 g, 4.08 mmol) and diisopropyl ethylamine (0.7 mL, 4.08 mmol) in methanol (10 mL) was heated under nitrogen to 40 °C for 16 hours before the solvent was removed in vacuo. The residue was subjected to column chromatography (SiO₂, Flash 40, petroleum ether/ethyl acetate 6:1) to give 0.70 g (36%) of a mixture of 2-amino-5-(S)-phenylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyridine-3,6-di-carboxylic acid di-*tert*-butyl ester and 2-amino-7-(R)-phenylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyridine-3,6-di-carboxylic acid di-*tert*-butyl ester isomers.

The above mixture was dissolved in dichloromethane (20 mL) and imidazole-1-yl-oxo-acetic acid *tert*-butyl ester (872 mg, 4.44 mmol) and triethylamine (618 μL, 4.44 mmol) was added. The reaction mixture was stirred 16 hours before the solvent was removed in vacuo and the residue was subjected to column chromatography (SiO₂, Flash 40, petroleum ether/ethyl acetate 5:1) to give 0.50 g (56%) as a mixture of 2-(*tert*-butoxyoxalyl-amino)-5-
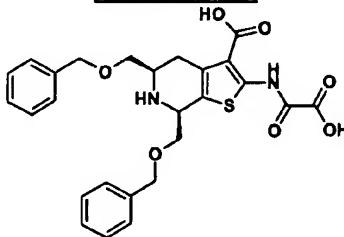
120

(S)-phenylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyridine-3,6-di-carboxylic acid di-*tert*-butyl ester and 2-(*tert*-butoxyoxalyl-amino)-7-(R)-phenylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyridine-3,6-di-carboxylic acid di-*tert*-butyl ester.

5   300 mg of the mixture was dissolved in a mixture of trifluoacetic acid/dichloromethane (1:1) (6.0 mL) and the solution was stirred for 16 hours at room temperature before the solvent was removed in vacuo. The residue was purified on preparative HPLC to give 70 mg (34%) of the title compound as a solid trifluoroacetate.

LC-MS; R_t = 0.95 min, m/z: 390 [M+H]$^+$

10   Calculated for $C_{17}H_{15}N_3O_6S$, $C_2HF_3O_2$, H_2O;

C, 43.77 %; H, 3.48 %; N, 8.06 %; Found:

C, 43.92 %; H, 3.44 %; N, 7.97 %.

15   EXAMPLE 52

5-(R),7-(R)-Bis-benzyloxymethyl-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

20   Benzyloxyacetaldehyde (0.90 g; 6.0 mmol) and dimethyl (2-oxomethyl)-phosphonate (1.0 g; 6.0 mmol) were dissolved in a mixture of tetrahydrofuran (25 ml) and water (20 ml). 1N Aqueous potassium hydroxide (6 ml) was added and the mixture was stirred for 30 min. Dichloromethane (50 ml) was added and the organic phase was separated, dried (MgSO$_4$) and evaporated in vacuo leaving 5-benzyloxypent-3-en-2-one.

25   ^{1}H-NMR: (CDCl$_3$): δ 2.25 (s, 3H); 4.19 (dd, 2H); 4.55 (s, 2H); 6.34 (dt; 1H); 6.70 (dt, 1H); 7.26 (m, 5H).

5-benzyloxypent-3-en-2-one was dissolved in methanol (5 ml) and ammonium acetate (13 mmol, 1.03 g) was mixted together with benzyloxyacetaldehyde (1.8 g; 12 mmol) and acetic acid (0.69 ml) and the mixture was stirred for 2 days. The solvent was removed in

30   vacuo and the residue was chromatographed on silica using gradient elution from 100 % dichloromethane to 100 % ethyl acetate. A fraction (411 mg) contained (according to LC-MS; m/z 340.4) 2,5-di(benzyloxymethyl)-4-piperidone in an impure state was isolated. The crude

mixture was dissolved in ethanol (3 ml) and *tert*-butylcyanoacetate (400 mg), sulfur (100 mg) and triethylamine was added and the mixture was stirred at room temperature overnight. The mixture was filtered and the solvent removed in vacuo. The residue was chromatographed on silica in a mixture of dichloromethane/(7% of 25% aqueous ammonia in ethanol) (40:1),

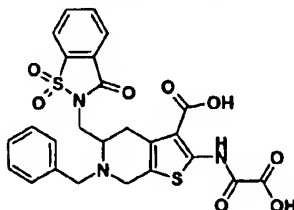5   which afforded 0.14 g of 2-amino-5-(*R*),7-(*R*)-bis-benzyloxymethyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester as an oil.

LC-MS: R_t: 6.03 min; m/z: 495.2 [M+H]$^+$

2-Amino-5-(*R*),7-(*R*)-Bis-benzyloxymethyl -4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid *tert*-butyl ester (0.14 g; 0.28 mmol) was dissolved in dichloromethane (5 ml)

10 and treated with imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.1 g; 0.5 mmol) and triethyl-amine (70 µl; 0.5 mmol), and stirred overnight, washed with water, dried (MgSO$_4$) and the solvent removed in vacuo. The residue was chromatographed on silica using ethyl ace-tate/dichloromethane (1:3) as eluent. The residue was treated with trifluoroacetic acid (0.5 ml) in dichloromethane (0.5 ml) and stirred for 4 hours. Evaporation of the solvent in vacuo

15 afforded 37 mg of the title compound.

LC-MS: R_t: 4.74 min; m/z: 511.4 [M+H]$^+$.

EXAMPLE 53

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6-Benzyl-2-(oxalyl-amino)-5-(1,1,3-trioxo-1,3-dihydro-1,6-benzo[d]isothiazol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid

1-Benzyl-4-oxo-piperidine-2-carboxylic acid ethyl ester (2.9 g; 11.1 mmol) (prepared in a

25 similar way as described in "GENERAL CHIRAL SYNTHESIS" for 4-oxo-1-((*S*)-1-phenyl-ethyl)-piperidine-(*R*)-2-carboxylic acid ethyl ester using benzylamine instead of 1-(*S*)-phenethylamine) was dissolved in abs. ethanol (50 ml) and sulfur (0.35 g, 11.1 mmol), triethylamine (1.6 ml, 11.1 mmol), and *tert*-butylcyanoacetate (1.7 g, 11.1 mmol) were added and the mixture was stirred 2 days at room temperature. The solvent was removed in vacuo

30 and the residue was chromatographed on silica using a mixture of ethyl actetate/heptane (1:4) as eleuent leaving a mixture (700 mg; 1:1 based on NMR) of 2-amino-6-benzyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,7-dicarboxylic acid 3-*tert*-butyl ester-7-ethyl ester and 2-

amino-6-benzyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,7-dicarboxylic acid 3-tert-butyl es-
ter 5-ethyl ester which was used in the next step without separation. To this mixture was
added tetrahydrofuran (5 ml) and lithium borohydride (1.1 ml of a 2M solution in tetrahydrofu-
ran) and the mixture was stirred 18 hours. More lithium borohydride (5.0 ml of a 2M solution

5   in tetrahydrofuran) was added and the mixture stirred for an additiona 4 days. Ethyl acetate
(10 ml) was added dropwise and after 1 hour the mixture was poured onto water (100 ml)
and extracted with dichloromethane (2 x 100 ml) and chromatographed on silica (using ethy-
lacetate/heptane 1:1 as eluent), which afforded a mixture of 2-amino-6-benzyl-7-
hydroxymethyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester and

10   2-amino-6-benzyl-5-hydroxymethyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid
tert-butyl ester (in total 187 mg). To this mixture was added dry tetrahydrofuran (10 ml), 2,3-
dihydro-1,2-benzisothiazol-3-one-1,1-dioxide (100 mg; 0.55 mmol), triphenylphosphine (144
mg 0.55 mmol) and the mixture was cooled with ice. Diethyl azodicarboxylate (86 µl) was
added and the mixture was stirred overnight at room temperature. The solvent was evapo-

15   rated in vacuo and the residue was chromatographed on silica using a mixture of ethyl ace-
tate/heptane (1:1) as eluent leaving 94 mg of 2-amino-6-benzyl-5-(1,1,3-trioxo-1,3-dihydro-
1,6-benzo[d]isothiazol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid
tert-butyl ester.

^{1}H-NMR: (CDCl$_3$): δ 1.52 (s, 9H); 2.75 (dd, 1H); 2.90 (dd, 1H); 3.55 (d, 1H); 3.72 (m,

20   4H); 3.94 (d, 1H); 4.12 (d, 1H); 5.97 (s, 2H); 7.14-7.37 (m, 5H); 7.80-8.03 (m, 4H).
LC-MS: R$_t$ 5.47 min, m/z: 540.4 [M+H]$^+$

2-Amino-6-benzyl-5-(1,1,3-trioxo-1,3-dihydro-1,6-benzo[d]isothiazol-2-ylmethyl)-
4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-butyl ester (94 mg; 0.17 mmol)
was dissolved in dichloromethane (5 ml) and treated with imidazol-1-yl-oxo-acetic acid tert-

25   butyl ester (0.07 g; 0.3 mmol) and triethylamine (49 µl; 0.3 mmol), and stirred overnight,
washed with water, 1N aqueous citric acid, dried (MgSO$_4$) and the solvent removed in vacuo
leaving 104 mg of 2-(tert-butoxyoxalyl-amino)-6-benzyl-5-(1,1,3-trioxo-1,3-dihydro-1,6-
benzo[d]isothiazol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-
butyl ester as an oil.

30   LC-MS : R$_t$: 5.50 min, m/z: 668.6 [M+H]$^+$

2-(tert-Butoxyoxalyl-amino)-6-benzyl-5-(1,1,3-trioxo-1,3-dihydro-1,6-
benzo[d]isothiazol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid tert-
butyl ester (100 mg; 0.15 mmol) was treated with trifluoroacetic acid (1 m) in dichloro-
methane (4 ml) and stirred for 2 days. Evaporation of the solvent in vacuo afforded 90 mg of

35   the title compound as a solid trifluoroacetate.

Calc. for $C_{25}H_{21}N_3O_8S_2$, $1.5xC_2HF_3O_2$, $0.5xH_2O$

C, 45.72%; H, 3.22%; N, 5.71%. Found:

C, 45.48%; H, 3.46%; N, 5.72%

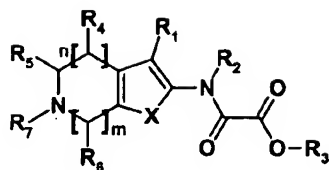LC-MS: R_t: 4.16 min; m/z: 556.2 $[M+H]^+$

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CLAIMS

1. A compound of Formula 1
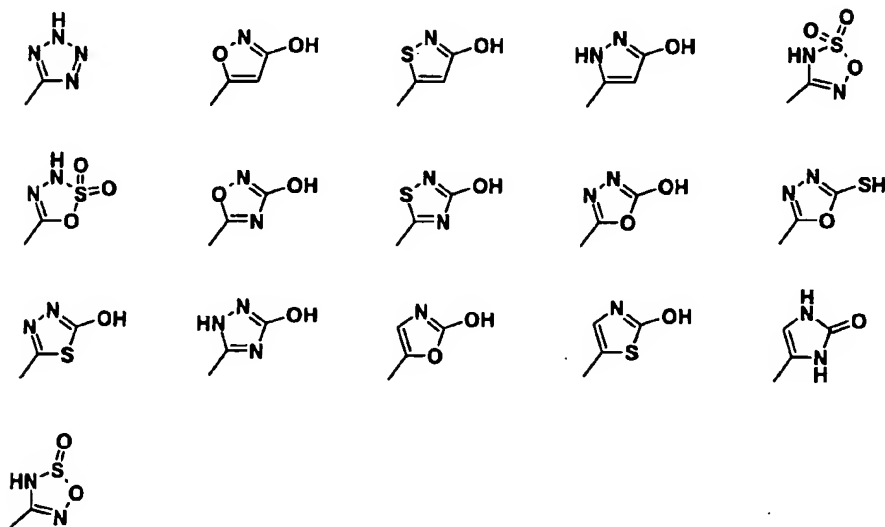

Formula 1

wherein

n is 0, 1 or 2;

m is 1 or 2;

X is S or O;

R_1 is hydrogen or $COOR_3$, or R_1 is selected from the group consisting of the following 5-membered heterocycles:

R_2 is hydrogen, C_1-C_6alkyl, hydroxy or NR_8R_9;

R_3 is hydrogen, C_1-C_6alkyl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyloxyC_1-C_6alkyl or C_1-C_6alkylcarbonyloxyarylC_1-C_6alkyl;

R_4, R_5 and R_6 are independently hydrogen, trihalomethyl, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, oxo, carboxy, carboxyC_1-C_6alkyl, C_1-C_6alkyloxy-carbonyl, aryloxycarbonyl, arylC_1-C_6alkyloxycarbonyl, C_1-C_6alkyloxy, C_1-C_6alkyloxyC_1-C_6alkyl, aryloxy, arylC_1-C_6alkyloxy, arylC_1-C_6alkyloxyC_1-C_6alkyl, thio, C_1-C_6alkyl-thio, C_1-C_6alkylthioC_1-C_6alkyl, arylthio, arylC_1-

5   C_6alkylthio, arylC_1-C_6alkylthioC_1-C_6alkyl, NR_8R_9, $R_8R_9NC_1$-C_6alkyl, C_1-C_6alkylaminoC_1-C_6alkyl, arylaminoC_1-C_6alkyl, arylC_1-C_6alkylaminoC_1-C_6alkyl, di(arylC_1-C_6alkyl)aminoC_1-C_6alkyl, C_1-C_6alkylcarbonyl, C_1-C_6alkylcarbonylC_1-C_6alkyl, arylC_1-C_6alkylcarbonyl, arylC_1-C_6alkylcarbonylC_1-C_6alkyl, C_1-C_6alkylcarboxy, C_1-C_6alkylcarboxyC_1-C_6-alkyl, arylcarboxy, arylcarboxyC_1-C_6alkyl, arylC_1-C_6alkylcarboxy, arylC_1-C_6alkyl-carboxyC_1-C_6alkyl, C_1-

10   C_6alkylcarbonylamino, C_1-C_6alkylcarbonylaminoC_1-C_6alkyl, -carbonylNR_8C_1-C_6alkylCOR_{12}, arylC_1-C_6alkylcarbonylamino, arylC_1-C_6alkyl-carbonylaminoC_1-C_6alkyl, arylcarbonylaminoC_1-C_6alkyl, $CONR_8R_9$, or C_1-C_6alkyl-$CONR_8R_9$ wherein the alkyl and aryl groups are optionally substituted as defined in the definition section and R_{12} is NR_8R_9, or C_1-C_6alkylNR_8R_9;

15   R_7 is hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, C_1-C_6alkyloxocarbonyl, arylcarbonyl, aryloxocarbonyl, arylC_1-C_6alkylcarbonyl, arylC_1-C_6alkyloxocarbonyl, C_1-C_6alkylcarboxy, arylC_1-C_6alkylcarboxy, $R_{10}R_{11}$NcarbonylC_1-C_6alkyl wherein R_{10} and R_{11} are independently selected from hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkyl-carbonyl, arylcarbonyl, arylC_1-C_6alkylcarbonyl, C_1-C_6alkylcarboxy or arylC_1-C_6alkylcarboxy; wherein the

20   alkyl and aryl groups are optionally substituted as defined in the definition section;

       R_8 and R_9 are independently selected from hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, C_1-C_6alkyloxocarbonyl, arylcarbonyl, aryloxocarbonyl, arylC_1-C_6alkylcarbonyl, arylC_1-C_6alkyloxocarbonyl, C_1-C_6alkylcarboxy, arylC_1-C_6alkylcarboxy,

25     $R_{10}R_{11}$NcarbonylC_1-C_6alkyl wherein the alkyl and aryl groups are optionally substituted as defined in the definition section; or
       R_8 and R_9 are together with the nitrogen to which they are attached forming a saturated, partially saturated or aromatic monocyclic, bicyclic or tricyclic ring system containing from 3 to 14 carbon atoms and from 0 to 3 additional heteroatoms selected from nitrogen, oxygen or

30   sulphur, the ring system can optionally be substituted with at least one C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, oxo, C_1-C_6alkyloxy, arylC_1-C_6alkyloxy, C_1-C_6alkyloxyC_1-C_6alkyl, $NR_{10}R_{11}$ or C_1-C_6alkyl-aminoC_1-C_6alkyl, wherein R_{10} and R_{11} are independently selected from hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, arylcarbonyl, arylC_1-C_6alkylcarbonyl, C_1-C_6alkylcarboxy or arylC_1-C_6alkylcarboxy; wherein the alkyl and aryl

35   groups are optionally substituted as defined in the definition section; or

R_8 and R_9 are independently a saturated or partial saturated cyclic 5, 6 or 7 membered amine, imide or lactam;

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form, or prodrug thereof.

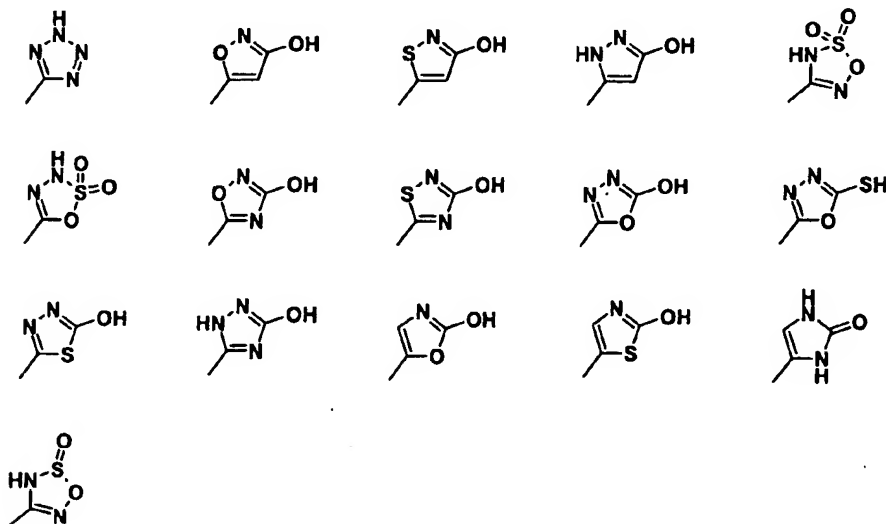2. A compound of Formula 1

Formula 1

wherein

n is 0, 1 or 2;

m is 1 or 2;

X is S or O;

R_1 is hydrogen or $COOR_3$, or R_1 is selected from the group consisting of the following 5-membered heterocycles:

R_2 is hydrogen, C_1-C_6alkyl, hydroxy or NR_8R_9;

R_3 is hydrogen, C_1-C_6alkyl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyloxyC_1-C_6alkyl or C_1-C_6alkylcarbonyloxyarylC_1-C_6alkyl;

5

R_4, R_5 and R_6 are independently hydrogen, trihalomethyl, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, oxo, carboxy, carboxyC_1-C_6alkyl, C_1-C_6alkyloxy-carbonyl, aryloxycarbonyl, arylC_1-C_6alkyloxycarbonyl, C_1-C_6alkyloxy, C_1-C_6alkyloxyC_1-C_6alkyl, aryloxy, arylC_1-C_6alkyloxy, arylC_1-C_6alkyloxyC_1-C_6alkyl, thio, C_1-C_6alkyl-thio, C_1-C_6alkylthioC_1-C_6alkyl, arylthio, arylC_1-

10　　C_6alkylthio, arylC_1-C_6alkylthioC_1-C_6alkyl, NR_8R_9, C_1-C_6alkylaminoC_1-C_6alkyl, arylC_1-C_6alkylaminoC_1-C_6alkyl, di(arylC_1-C_6alkyl)aminoC_1-C_6alkyl, C_1-C_6alkylcarbonyl, C_1-C_6alkylcarbonylC_1-C_6alkyl, arylC_1-C_6alkylcarbonyl, arylC_1-C_6alkylcarbonylC_1-C_6alkyl, C_1-C_6alkyl-carboxy, C_1-C_6alkylcarboxyC_1-C_6-alkyl, arylcarboxy, arylcarboxyC_1-C_6alkyl, arylC_1-C_6alkylcarboxy, arylC_1-C_6alkylcarboxyC_1-C_6alkyl, C_1-C_6alkylcarbonylamino, C_1-

15　　C_6alkylcarbonylaminoC_1-C_6alkyl, -carbonylNR_8C_1-C_6alkylCOR_{12}, arylC_1-C_6alkylcarbonyl-amino, arylC_1-C_6alkylcarbonylaminoC_1-C_6alkyl, $CONR_8R_9$, or C_1-C_6alkyl-$CONR_8R_9$ wherein the alkyl and aryl groups are optionally substituted and R_{12} is NR_8R_9, or C_1-C_6alkylNR_8R_9;

R_7 is hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, C_1-C_6alkyloxocarbonyl,

20　　arylcarbonyl, aryloxocarbonyl, arylC_1-C_6alkylcarbonyl, arylC_1-C_6alkyloxocarbonyl, C_1-C_6alkylcarboxy, arylC_1-C_6alkylcarboxy, $R_{10}R_{11}$NcarbonylC_1-C_6alkyl wherein R_{10} and R_{11} are independently selected from hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, arylcarbonyl, arylC_1-C_6alkylcarbonyl, C_1-C_6alkylcarboxy or arylC_1-C_6alkylcarboxy; wherein the alkyl and aryl groups are optionally substituted;

25

R_8 and R_9 are independently selected from hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, C_1-C_6alkyloxocarbonyl, arylcarbonyl, aryloxocarbonyl, arylC_1-C_6alkylcarbonyl, arylC_1-C_6alkyloxocarbonyl, C_1-C_6alkylcarboxy, arylC_1-C_6alkylcarboxy, $R_{10}R_{11}$NcarbonylC_1-C_6alkyl wherein the alkyl and aryl groups are optionally substituted; or

30　　R_8 and R_9 are together with the nitrogen to which they are attached forming a saturated, partially saturated or aromatic cyclic, bicyclic or tricyclic ring system containing from 3 to 14 carbon atoms and from 0 to 3 additional heteroatoms selected from nitrogen, oxygen or sulphur, the ring system can optionally be substituted with at least one C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, oxo, C_1-C_6alkyloxy, arylC_1-C_6alkyloxy, C_1-C_6alkyloxyC_1-C_6alkyl, $NR_{10}R_{11}$ or C_1-

35　　C_6alkylaminoC_1-C_6alkyl, wherein R_{10} and R_{11} are independently selected from hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, arylcarbonyl, arylC_1-C_6alkylcarbonyl, C_1-

C_6alkylcarboxy or arylC_1-C_6alkylcarboxy; wherein the alkyl and aryl groups are optionally substituted ; or

R_8 and R_9 are independently a saturated or partial saturated cyclic 5, 6 or 7 membered amine, imide or lactam;

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form.

3. A compound according to claim 2 wherein X is sulphur.

4. A compound according to claim 3 wherein R_1 is $COOR_3$ and R_2 is hydrogen; wherein R_3 is defined as above.

5. A compound according to claim 4 wherein n and m are 1.

6. A compound according to claims 4 or 5 wherein R_5 is C_1-C_6alkylNR_8R_9.

7. A compound according to claim 6 wherein R_4 and R_6 are hydrogen.

8. A compound according to claim 3 wherein R_1 is 5-tetrazolyl, R_2 is hydrogen, and R_5 is C_1-C_6alkylNR_8R_9.

9. A compound according to claim 4 or 5 wherein R_6 is C_1-C_6alkylNR_8R_9.

10. A compound according to claim 9 wherein R_4 and R_5 are hydrogen.

11. A compound according to claim 3 wherein R_1 is 5-tetrazolyl, R_2 is hydrogen, and R_6 is C_1-C_6alkylNR_8R_9.

12. A compound according to claim 3 wherein R_5 and R_6 are C_1-C_6alkylNR_8R_9.

13. A compound according to claim 12 wherein R_1 is $COOR_3$ and R_2 is hydrogen; wherein R_3 is defined as above.

14. A compound according to claim 13 wherein n and m are 1.

15. A compound according to claim 12 wherein R_1 is 5-tetrazolyl.

16. A compound according to claim 6 and 7 wherein R_8 and R_9 are together with the nitrogen

5   to which they are attached forming a partially saturated bicyclic ring system containing 8 carbon atoms, the ring system being optionally substituted with two oxo groups.

17. A compound according to claim 16 wherein the ring system is isoindolyl.

10   18. A compound according to claim 17 wherein R_7 is C_1-C_6alkyloxocarbonyl.

19. A compound according to claim 9 and 10 wherein R_8 and R_9 are together with the nitrogen to which they are attached forming a partially saturated bicyclic ring system containing 8 carbon atoms, the ring system being optionally substituted with two oxo groups.

15

20. A compound according to claim 19 wherein the ring system is isoindolyl.

21. A compound according to claim 9 and 10 wherein R_8 and R_9 are together with the nitrogen to which they are attached forming a partially saturated bicyclic ring system containing 7

20   carbon atoms and one sulfur atom, the ring system being optionally substituted with three oxo groups.

22. A compound according to claim 21 wherein the ring system is 2,3-dihydro-benzo[d]iosthiazolyl.

25

23. A compound according to claim 9 and 10 wherein R_8 and R_9 are together with the nitrogen to which they are attached forming a partially saturated bicyclic ring system containing 7 carbon atoms and one sulfur atom, the ring system being optionally substituted with two oxo groups.

30

24. A compound according to claim 21 wherein the ring system is 2,3-dihydro-benzo[d]iosthiazolyl.

25. A compound according to claim 20 wherein R_7 is C_1-C_6alkyloxocarbonyl.

35

26. A compound according to claim 9 and 10 wherein R_8 and R_9 are together with the nitrogen to which they are attached forming a partially saturated bicyclic ring system containing 8 carbon atoms, the ring system being optionally substituted with one oxo group.

5   27. A compound according to claim 22 wherein the ring system is optionally substituted isoindolyl.

28. A compound according to claim 22 wherein the ring system is optionally substituted 1-oxo-1,3-dihydro-isoindolyl.

10

29. A compound according to claim 22 wherein R_7 is C_1-C_6alkyloxocarbonyl.

30. A compound according to claims 4 or 5 wherein R_5 and R_6 are C_1-C_6alkylNR$_8$R$_9$.

15   31. A compound according to any one of the preceding claims wherein X is sulphur.

32. A compound according to any one of the preceding claims wherein R_1 is COOR$_3$ and R_2 ishydrogen; wherein R_3 is defined as above.

20   33. A compound according to any one of the preceding claims wherein n and m are 1.

34. A compound according to any one of the preceding claims wherein R_5 is C_1-C_6alkylNR$_8$R$_9$.

25   35. A compound according to any one of the preceding claims wherein R_4 and R_6 are hydrogen.

36. A compound according to any one of the preceding claims wherein R_1 is 5-tetrazolyl, R_2 is hydrogen, and R_5 is C_1-C_6alkylNR$_8$R$_9$.

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37. A compound according to any one of the preceding claims wherein R_6 is C_1-C_6alkylNR$_8$R$_9$.

38. A compound according to any one of the preceding claims wherein R_4 and R_5 are hydrogen.

35   gen.

39. A compound according to any one of the preceding claims wherein R_1 is 5-tetrazolyl, R_2 is hydrogen, and R_6 is C_1-C_6alkylNR$_8$R$_9$.

40. A compound according to any one of the preceding claims wherein R_5 and R_6 are C_1-C_6alkylNR$_8$R$_9$.

41. A compound according to any one of the preceding claims wherein R_1 is COOR$_3$ and R_2 is hydrogen; wherein R_3 is defined as above.

42. A compound according to any one of the preceding claims wherein n and m are 1.

43. A compound according to any one of the preceding claims wherein R_1 is 5-tetrazolyl.

44. A compound according to any one of the preceding claimswherein R_8 and R_9 are together with the nitrogen to which they are attached forming a partially saturated bicyclic ring system containing 8 carbon atoms, the ring system being optionally substituted with two oxo groups.

45. A compound according to any one of the preceding claims wherein the ring system is isoindolyl.

46. A compound according to any one of the preceding claims wherein R_7 is C_1-C_6alkyloxo-carbonyl.

47. A compound according to any one of the preceding claims wherein R_8 and R_9 are to-gether with the nitrogen to which they are attached forming a partially saturated bicyclic ring system containing 8 carbon atoms, the ring system being optionally substituted with two oxo groups.

48. A compound according to any one of the preceding claims wherein the ring system is isoindolyl.

49. A compound according to any one of the preceding claims wherein R_8 and R_9 are to-gether with the nitrogen to which they are attached forming a partially saturated bicyclic ring system containing 7 carbon atoms and one sulfur atom, the ring system being optionally substituted with three oxo groups.

50. A compound according to any one of the preceding wherein the ring system is 2,3-dihydro-benzo[d]iosthiazolyl.

5   51. A compound according to any one of the preceding claims wherein R_8 and R_9 are together with the nitrogen to which they are attached forming a partially saturated bicyclic ring system containing 7 carbon atoms and one sulfur atom, the ring system being optionally substituted with two oxo groups.

52. A compound according to any one of the preceding claims wherein the ring system is
10   2,3-dihydro-benzo[d]iosthiazolyl.

53. A compound according to any one of the preceding claims wherein R_7 is C_1-C_6alkyloxocarbonyl.

15   54. A compound according to any one of the preceding claims wherein R_8 and R_9 are together with the nitrogen to which they are attached forming a partially saturated bicyclic ring system containing 8 carbon atoms, the ring system being optionally substituted with one oxo group.

20   55. A compound according to any one of the preceding claims wherein the ring system is optionally substituted isoindolyl.

56. A compound according to any one of the preceding claims wherein the ring system is optionally substituted 1-oxo-1,3-dihydro-isoindolyl.
25

57. A compound according to any one of the preceding claims wherein R_7 is C_1-C_6alkyloxocarbonyl.

58. A compound according to any one of the preceding claims wherein R_5 and R_8 are C_1-
30   C_6alkylNR_8R_9.

59. A compound according to any one of the preceding claims wherein R_5 is 1,3-dihydro-isoindol, substituted with 1 or 2 oxo groups at the atom positions adjacent to the nitrogen atom and optionally substituted with hydroxy, C_{1-6}-alkyloxy, arylC_{1-6}-alkyloxy or C_{1-6}-
35   alkylcarboxy, and wherein R_7 is hydrogen, alkyl, alkyloxycarbonyl, arylalkyl or aryl wherein aryl is optionally substituted with methoxy.

60. A compound according to any one of the preceding claims wherein R_5 is 1,1,3-trioxo-1,2-dihydro-1H-benzo[d]isothiazol-2-yl and wherein R_7 is hydrogen or arylalkyl.

61. A compound according to any one of the preceding claims wherein R_5 or R_6 is arylaminoalkyl, wherein aryl is 1,1-dioxo-1,2-dihydro-1H-benzo[d]isothiazol-3-yl.

62. A compound according to any one of the preceding claims R_5 or R_6 is arylcarbonylaminoalkyl, wherein aryl is phenyl, indol-3-yl, indol-2-yl, 1,2,3-triazol-4-yl, quinolin-4-yl or naphth-1-yl wherein aryl is optionally substituted, and wherein R_7 is hydrogen or arylalkyl optionally substituted with methoxy.

63. A compound according to any one of the preceding claims wherein R_5 is arylalkylaminoalkyl wherein aryl is phenyl, dibenzofuranyl, naphth-2-yl or indo-3-yl, and wherein alkyl and aryl are optionally substituted, and wherein R_7 is hydrogen or arylalkyl optionally substituted with methoxy.

64. A compound according to any one of the preceding claims wherein R_6 is alkylNR_8R_9, wherein R_8 is alkylcarbonyl and R_9 is arylalkyl, wherein aryl is optionally substituted.

65. A compound according to claim 1 or 2 selected from the following:

5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid 6-ethyl ester;

5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

(L)-5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(4-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-5-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-7-(1,1,3-trioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-(1,1-Dioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-
thieno[2,3-c]pyridine-3-carboxylic acid;

5

or a pharmaceutically acceptable salt thereof.

66. A compound according to claim 1 or 2 selected from the following:

10   5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-
c]pyridine-3,6-dicarboxylic acid 6-ethyl ester;

5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-
c]pyridine-3-carboxylic acid;

(S)-5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-
15   thieno[2,3-c]pyridine-3-carboxylic acid;

7-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-
c]pyridine-3-carboxylic acid;

5-(4-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-
thieno[2,3-c]pyridine-3-carboxylic acid;

20   2-(Oxalyl-amino)-5-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-
c]pyridine-3-carboxylic acid;

5-(4-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-
thieno[2,3-c]pyridine-3-carboxylic acid;

5-(4-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-methyl-2-(oxalyl-amino)-4,5,6,7-
25   tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-((1,1-Dioxo-1H-benzo[d]isothiazol-3-ylamino)-methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-
thieno[2,3-c]pyridine-3-carboxylic acid;

7-((1,1-Dioxo-1H-benzo[d]isothiazol-3-ylamino)-methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-
thieno[2,3-c]pyridine-3-carboxylic acid;

30   5-(7-Methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-
thieno[2,3-c]pyridine-3-carboxylic acid;

5-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-
thieno[2,3-c]pyridine-3-carboxylic acid;

5-(7-Benzyloxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-
35   thieno[2,3-c]pyridine-3-carboxylic acid;

5-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-
4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5   7-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-
thieno[2,3-c]pyridine-3-carboxylic acid;

7-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-
4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-

10   tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(S)-(7-Methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-
thieno[2,3-c]pyridine-3-carboxylic acid;

5-(R)-(7-Methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-
thieno[2,3-c]pyridine-3-carboxylic acid;

15   5-(4-Benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(6-Methoxy-4-methoxycarbonyl-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-
4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-5-(1,1,3-trioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-

20   5H-thieno[2,3-c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-7-(1,1,3-trioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-
5H-thieno[2,3-c]pyridine-3-carboxylic acid;

7-Carbamoyl-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-5-(2-oxo-tetrahydro-thiophen-3-ylcarbamoyl)-4,5,6,7-tetrahydro-thieno[2,3-

25   c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-5-phenylcarbamoyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic
acid;

2-(Oxalyl-amino)-7-phenylcarbamoyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic
acid;

30

or a pharmaceutically acceptable salt thereof.

67. A compound according to claim 1 or 2 selected from the following:

35   5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-
c]pyridine-3,6-dicarboxylic acid 6-ethyl ester;

136

5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(S)-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5   7-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(4-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-thieno[2,3-c]pyridine-3-carboxylic acid;

7-(4-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-

10   thieno[2,3-c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-5-(S)-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(4-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

15   5-(4-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-methyl-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-((1,1-Dioxo-1H-benzo[d]isothiazol-3-ylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-((1,1-Dioxo-1H-benzo[d]isothiazol-3-ylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-

20   thieno[2,3-c]pyridine-3-carboxylic acid;

5-(7-Methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

25   5-(7-Benzyloxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-

30   tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

35   7-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-(((5-Benzyloxy-1*H*-indole-2-carbonyl)amino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-
4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-(((6-Bromo-2-p-tolyl-quinoline-4-carbonyl)amino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-
amino)- 4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5   6-(4-Methoxy-benzyl)-7-(((5-methyl-2-phenyl-2*H*-[1,2,3]triazole-4-carbonyl)amino)methyl)-2-
(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-(((1*H*-Indole-3-carbonyl)amino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-((4-Ethoxy-2-hydroxy-benzoylamino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-

10   4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-((4-Benzoylamino-benzoylamino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-(((Biphenyl-4-carbonyl)-amino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

15   7-(((1*H*-Indole-2-carbonyl)amino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-((3-Biphenyl-4-yl-acryloylamino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-
tetrahydro-thieno[2,3-c)pyridine-3-carboxylic acid;

6-(4-Methoxy-benzyl)-7-(((5-methoxy-1*H*-indole-2-carbonyl)amino)methyl)-2-(oxalyl-amino)-

20   4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

7-((4-Benzyl-benzoylamino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

6-(4-Methoxy-benzyl)-7-(((naphthalene-1-carbonyl)amino)methyl)-2-(oxalyl-amino)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

25   6-(4-Methoxy-benzyl)-5-((2-naphthalen-2-yl-ethylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-((2-Benzo[1,3]dioxol-5-yl-acetylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-
thieno[2,3-c]pyridine-3-carboxylic acid;

5-((2-Dibenzofuran-2-yl-ethyl)amino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-

30   tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

6-(4-Methoxy-benzyl)-5-((2-(5-methoxy-2-methyl-1*H*-indol-3-yl)-acetylamino)methyl)-2-
(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-((2-(1*H*-Indol-3-yl)-2-oxo-acetylamino)methyl)-2-(Oxalyl-amino)-4,5,6,7-tetrahydro-
thieno[2,3-c]pyridine-3-carboxylic acid;

35   5-(*R*)-(7-Methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-
thieno[2,3-c]pyridine-3-carboxylic acid;

5-(S)-(7-Methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-
thieno[2,3-c]pyridine-3-carboxylic acid;

5-(S)-(4-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-
thieno[2,3-c]pyridine-3-carboxylic acid;

5   2-(S)-(Oxalyl-amino)-5-((4-phenoxy-benzylamino)methyl)-4,5,6,7-tetrahydro-thieno[2,3-
c]pyridine-3-carboxylic acid;

5-(S)-((4-Acetylamino-benzylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-
c]pyridine-3-carboxylic acid;

7-(S)-((Acetyl-(4-phenoxy-benzyl)amino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-

10   thieno[2,3-c]pyridine-3-carboxylic acid;

7-(S)-((Acetyl-benzyl-amino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-
3-carboxylic acid;

5-(S)-((1,1-Dioxo-1H-benzo[d]isothiazol-3-ylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

15   5-(4-Benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-
tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

5-(6-Methoxy-4-methoxycarbonyl-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-
4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-5-(1,1,3-trioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-

20   5H-thieno[2,3-c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-7-(1,1,3-trioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-
5H-thieno[2,3-c]pyridine-3-carboxylic acid;

7-(R)-Carbamoyl-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-5-(S)-(2-oxo-tetrahydro-thiophen-3-ylcarbamoyl)-4,5,6,7-tetrahydro-

25   thieno[2,3-c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-5-(S)-phenylcarbamoyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic
acid;

2-(Oxalyl-amino)-7-(R)-phenylcarbamoyl-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic ·
acid;

30   5-(R),7-(R)-Bis-benzyloxymethyl-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-
carboxylic acid;

6-Benzyl-2-(oxalyl-amino)-5-(1,1,3-trioxo-1,3-dihydro-1,6-benzo[d]isothiazol-2-ylmethyl)-
4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form, or prodrug thereof.

5   68. Compounds according to any one of the preceding claims which acts as inhibitors of Protein Tyrosine Phosphatases.

69. A pharmaceutical composition comprising a compound according to any of the claims 1 to 67 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid
10   or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form together with one or more pharmaceutically acceptable carriers or diluents.

70. A pharmaceutical composition suitable for treating type I diabetes, type II diabetes, impai-
15   red glucose tolerance, insulin resistance or obesity comprising a compound according to any of the claims 1 to 67 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form together with one or more pharmaceutically acceptable carriers or diluents.

20

71. A pharmaceutical composition suitable for treating immune dysfunctions including autoimmunity, diseases with dysfunctions of the coagulation system, allergic diseases, osteoporosis, proliferative disorders including cancer and psoriasis, diseases with decreased or increased synthesis or effects of growth hormone, diseases with decreased or increased
25   synthesis of hormones or cytokines that regulate the release of/or response to growth hormone, diseases of the brain including Alzheimer's disease and schizophrenia, and infectious diseases comprising a compound according to any of the claims 1 to 67 or a pharmaceutical acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form to-
30   gether with one or more pharmaceutically acceptable carriers or diluents.

72. The pharmaceutical composition according to claim 69, 70 or 71 in the form of an oral dosage unit or parenteral dosage unit.

140

73. A pharmaceutical composition according to claim 69, 70 or 71 wherein said compound is administered as a dose in a range from about 0.05 to 1000 mg, preferably from about 0.1 to 500 mg and especially in the range from 50 to 200 mg per day.

5   74. A compound according to any one of the claims 1 to 67 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for therapeutical use.

75. A compound according to any one of the claims 1 to 67 or a pharmaceutically acceptable
10   salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for therapeutical use in the treatment or preventing of type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance or obesity.

15   76. A compound according to any one of the claims 1 to 67 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for therapeutical use in the treatment or preventing of immune dysfunctions including autoimmunity, diseases with dysfunctions of the coagulation system, allergic diseases, osteoporosis, proliferative
20   disorders including cancer and psoriasis, diseases with decreased or increased synthesis or effects of growth hormone, diseases with decreased or increased synthesis of hormones or cytokines that regulate the release of/or response to growth hormone, diseases of the brain including Alzheimer's disease and schizophrenia, and infectious diseases.

25   77. The use of a compound according to any one of the claims 1 to 67 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form as a medicament.

30   78. The use of a compound according to any of the claims 1 to 67 for preparing a medicament.

79. The use of a compound according to any one of the claims 1 to 67 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical
35   isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for

the preparation of a medicament suitable for the treatment or preventing of type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance or obesity.
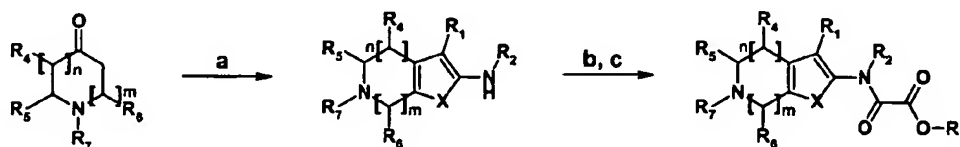
80. The use of a compound according to any one of the claims 1 to 67 or a pharmaceutically
5   acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for the preparation of a medicament suitable for the treatment or preventing of immune dysfunctions including autoimmunity, diseases with dysfunctions of the coagulation system, allergic diseases, osteoporosis, proliferative disorders including cancer and psoriasis,
10   diseases with decreased or increased synthesis or effects of growth hormone, diseases with decreased or increased synthesis of hormones or cytokines that regulate the release of/or response to growth hormone, diseases of the brain including Alzheimer's disease and schizophrenia, and infectious diseases.

15   81. A method of treating type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance or obesity comprising administering to a subject in need thereof an effective amount of a compound according to any of the claims 1 to 67 to said subject.

82. A method of treating immune dysfunctions including autoimmunity, diseases with
20   dysfunctions of the coagulation system, allergic diseases, osteoporosis, proliferative disorders including cancer and psoriasis, diseases with decreased or increased synthesis or effects of growth hormone, diseases with decreased or increased synthesis of hormones or cytokines that regulate the release of/or response to growth hormone, diseases of the brain including Alzheimer's disease and schizophrenia, and infectious diseases comprising
25   administering to a subject in need thereof an effective amount of a compound according to any of the claims 1 to 67 to said subject.

83. A process for the manufacture of a medicament, particular to be used in the treatment or prevention of type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance
30   or obesity which process comprising bringing a compound according to any of the claims 1 to 67 or a pharmaceutically acceptable salt thereof into a galenic dosage form.

84. A process for the manufacture of a medicament, particular to be used in the treatment or prevention of immune dysfunctions including autoimmunity, diseases with dysfunctions of the
35   coagulation system, allergic diseases, osteoporosis, proliferative disorders including cancer and psoriasis, diseases with decreased or increased synthesis or effects of growth hormone,

diseases with decreased or increased synthesis of hormones or cytokines that regulate the release of/or response to growth hormone, diseases of the brain including Alzheimer's disease and schizophrenia, and infectious diseases which process comprising bringing a compound according to any of the claims 1 to 67 or a pharmaceutically acceptable salt

5   thereof into a galenic dosage form.

85. Any novel feature or combination of features as described herein.

86. A method for preparing a compound of formula 1, characterized in

10   **A)**

a) $NCCH_2COOR_3$, sulphur, morpholine or triethylamine, ethanol; b) R_3OCOCOimidazole, tet-

15   rahydrofuran; c) 25 % trifluoroacetic acid/dichloromethane; wherein n, m, X, R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are defined above, or

B)

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By allowing an amine (I) and a substituted oxalylamide (II) to react under basic conditions (e.g. K_2CO_3, in N,N-dimethylformamide or methylethylketone) or under Mitsunobu conditions (Oyo Mitsunobu, Synthesis, (1981) 1-28) to yield (III) wherein W is OH, OSO_2Me or halo, and n, m, X, R_1, R_2, R_3, R_4, R_6, R_7 and R_8 are defined above, or

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C)

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By allowing an amine (I) and a substituted oxalylamide (II) to react under basic conditions (e.g. K_2CO_3, in N,N-dimethylformamide or methylethylketone) or under Mitsunobu conditions (Oyo Mitsunobu, *Synthesis*, (1981) 1-28) to yield (III) wherein W is OH, OSO_2Me or halo, and

5   n, m, X, R_1, R_2, R_3, R_4, R_5, R_7 and R_8 are defined above.

87. A pharmaceutical composition suitable for treating type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance or obesity comprising a compound according to any of the claims 1 to 67 or a pharmaceutical acceptable salt thereof with a pharmaceutically

10   acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form together with one or more pharmaceutically acceptable carriers or diluents and an insulin sensitizer, such as a thiazolidinedione eg. troglitazone, ciglitazone, pioglitazone, rosiglitazone, 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione or a pharmaceutically acceptable

15   salt thereof, preferably the potassium salt, or (-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or a pharmaceutically acceptable salts thereof, preferably the arginine salt.

88. The use of a compound according to any one of the claims 1 to 67 or a pharmaceutically

20   acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form and an insulin sensitizer, such as a thiazolidinedione eg. troglitazone, ciglitazone, pioglitazone, rosiglitazone, 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione or a pharmaceutically acceptable salt thereof, preferably the

25   potassium salt, or (-) 3-[4-[2-Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or a pharmaceutically acceptable salts thereof, preferably the arginine salt for the preparation of a medicament suitable for the treatment or preventing of type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance or obesity.

30   89. A method of treating type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance or obesity comprising administering to a subject in need thereof an effective amount of a compound according to any of the claims 1 to 67 and an insulin sensitizer, such as a thiazolidinedione eg. troglitazone, ciglitazone, pioglitazone, rosiglitazone, 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione or a

35   pharmaceutically acceptable salt thereof, preferably the potassium salt, or (-) 3-[4-[2-

Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or a pharmaceutically acceptable salts thereof, preferably the arginine salt to said subject.

90. A pharmaceutical composition suitable for treating type I diabetes, type II diabetes, im-
5   paired glucose tolerance, insulin resistance or obesity comprising a compound according to any of the claims 1 to 67 or a pharmaceutical acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form together with one or more pharmaceutically acceptable carriers or diluents and an agent stimulating insulin release from β cells such as repag-
10   linide.

91. The use of a compound according to any one of the claims 1 to 67 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form and
15   an agent stimulating insulin release from β cells such as repaglinide for the preparation of a medicament suitable for the treatment or preventing of type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance or obesity.

92. A method of treating type I diabetes, type II diabetes, impaired glucose tolerance, insulin
20   resistance or obesity comprising administering to a subject in need thereof an effective amount of a compound according to any of the claims 1 to 67 and an agent stimulating insulin release from β cells such as repaglinide to said subject.

93. A pharmaceutical composition suitable for treating type I diabetes, type II diabetes, im-
25   paired glucose tolerance, insulin resistance or obesity comprising a compound according to any of the claims 1 to 67 or a pharmaceutical acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form together with one or more pharmaceutically acceptable carriers or diluents and an antiobesity agent such as orlistat.
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94. The use of a compound according to any one of the claims 1 to 67 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form and an and an antiobesity agent such as orlistat for the preparation of a medicament suitable for
35   the treatment or preventing of type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance or obesity.

95. A method of treating type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance or obesity comprising administering to a subject in need thereof an effective amount of a compound according to any of the claims 1 to 67 and an antiobesity agent such as orlistat to said subject.

INTERNATIONAL SEARCH REPORT

	International application No.
	PCT/DK 00/00502

A. CLASSIFICATION OF SUBJECT MATTER IPC7: C07D 495/04, C07D 491/04, A61K 31/4365,
A61K 31/4355, A61P 3/00, A61P 5/00, A61P 7/00, A61P 17/00, A61P 19/00,
A61P 25/00, A61P 31/00, A61P 35/00, A61P 37/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 9946267 A1 (NOVO NORDISK A/S ET AL), 16 Sept 1999 (16.09.99) --	1-95
P,X	WO 9946237 A1 (NOVO NORDISK A/S ET AL), 16 Sept 1999 (16.09.99) --	1-95
P,X	WO 9946268 A1 (NOVO NORDISK A/S ET AL), 16 Sept 1999 (16.09.99) --	1-95

[X] Further documents are listed in the continuation of Box C.   [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 January 2000	23. 02. 2001

| Name and mailing address of the International Searching Authority European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel(+31-70)340-2040, Tx 31 651 epo nl, Fax(+31-70)340-3016 | Authorized officer NEBIL GECER/GH Telephone No. |

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 00/00502

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	THE JOURNAL OF BIOLOGICAL CHEMISTRY, Volume 275, No 14, April 2000, Lars Fogh Iversen, et al, "Structure-based Design of a Low Molecular Weight, Nonphosphorus, Nonpeptide, and Highly Selective Inhibitor of Protein-tyrosine Phosphatase 1B", page 10300 - page 10307 --	1-95
P,X	THE JOURNAL OF BIOLOGICAL CHEMISTRY, Volume 275, No 24, June 2000, Günter H. Peters, et al, "Residue 259 Is a Key Determinant of Substrate Specificity of Protein-tyrosine Phosphatases 1B and ‚alpha.", page 18201 - page 18209 --	1-95
A	US 3953468 A (WILLIAN J. WECHTER ET AL), 27 April 1976 (27.04.76) --	1-95
A	GB 1583679 A (BRISTOL-MYERS COMPANY), 28 January 1981 (28.01.81), see formula IV -- ---------	1-95

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK00/00502

| Box I | Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet) |

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 77,81-82,89,92,95
because they relate to subject matter not required to be searched by this Authority, namely:

   see next sheet *

2. ☒ Claims Nos.: 85
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

   Claim 85 does not comply with Art. 6 PCT prescribing that claims shall be clear and concise. The subject matter for which protection is sought is not defined.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

| Box II | Observations where unity of invention is lacking (Continuation of item 2 of first sheet) |

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest   ☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July1998)

Claims 77,81-82,89,92,95 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/ Rule. 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds.